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SOME RECENT WORK ON INHIBITION.

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THE nature of inhibition, by which the excitation of a nerve cuts short the activity of the structures to which it leads, has been one of the classical problems of physiology since the action of the vagus was first discovered, and Sherrington has demonstrated the fundamental part it plays in the working of the central nervous system. It cannot be said that we are much nearer a solution of the problem in terms of physics and chemistry, but recent work has opened up several promising fields, and the facts collected have at least made it easier to see what lines of advance are worth following. The present review attempts to summarize some of these facts; it will have failed in its purpose if it gives the impression that we have a satisfactory explanation of any form of inhibition, but the danger of this is not acute.

Out of many theories of inhibition there are two which have taken definite shape in recent years. In one of these the inhibition is supposed to be due to the formation of a special inhibiting substance at a synapse or myoneural junction. Its chief support comes from the effects of drugs such as adrenalin on plain muscle. Adrenalin can certainly play the rôle of an "inhibiting substance" which cuts short the activity of a muscle cell, and according to the most recent development of the theory there is evidence of a vagal substance with an inhibitory effect upon heart muscle. The other general theory is that put forward by Verworn, and with important modifications by Keith Lucas who based his suggestion on an analysis of what is known as "Wedensky inhibition" in the isolated muscle-nerve preparation. According to this view the inhibition is due to the refractory state which follows an impulse in any excitable tissue and the effect is produced by a particular arrangement of conducting paths which prevents

the inhibiting impulse from reaching the nerve cell or muscle, but allows it to leave a refractory state which blocks the path of other impulses. It should be noted that both theories agree in assuming that the disturbance which travels along the inhibiting nerve-fibre has no specific properties which would distinguish it from the normal excitatory disturbance. It is called into play by the same kind of stimuli, it travels at the same rate, and the results of nerve regeneration show that inhibitory and excitatory fibres are to some extent interchangeable. Inhibition, then, seems to be produced by the normal type of impulse, travelling in the normal type of nerve-fibre, and it is only when the myoneural junction or the synaptic region of the central nervous system is encountered that the specific conditions arise which make the impulse give an inhibitory instead of an excitatory effect. This conclusion alone is of considerable importance and there seems to be little doubt of its validity.

When we come to the rival merits of the two theories, there is some doubt as to whether they are really rivals after all, for the "inhibiting substance" theory (and the "humoral" theory of Loewi and others) derives all its evidence from the peripheral inhibition of cardiac or plain muscle, whereas the theory which relates inhibition to the refractory state has so far been applied only to the central nervous system. The truth may lie in a fusion of the two, or in some entirely different conception; but there is also the possibility that there may be several kinds of inhibition. There are more ways than one of cutting short an excitation, and different inhibitory mechanisms may have evolved alongside one another to suit the different conditions of the skeletal and visceral nervous systems.

Peripheral Inhibition.

The humoral theory.—The parallelism between the effects of adrenalin and of sympathetic stimulation has given rise to much speculation and is, of course, the corner-stone of much of the theory of endocrinology. The usual explanation is that the effects of adrenalin and of the sympathetic impulse are alike because both of them act on the same specialized receptive substance or mechanism in the muscle fibre. Another possibility which has often been discussed is that adrenalin or something like it is an essential link in the sympathetic chain—that the impulse acts by liberating adrenalin and that the characteristic effects of sympathetic stimulation are really the characteristic effects of adrenalin. There are various difficulties in the way

of such an explanation [2], but something very much like it has come to the front again in connection with Loewi's work on the vagus. Loewi has found [20, 21] that the fluid coming from a heart which has been inhibited by vagal stimulation has the property of inhibiting another heart into which it is introduced. The two hearts may be perfused in series with some form of Ringer's fluid, or a crossed circulation may be established between two animals. In either case the effects of the vagus on the one heart are followed by similar effects on the other heart although the vagus of the latter has not been touched. Sympathetic stimulation is said to yield a fluid which will reproduce the sympathetic effect in the same way, and Brinkman and van Dam [4, 5] have coupled the heart of one frog to the vessels supplying the stomach of another frog and find that vagal stimulation of the heart causes increased movement of the stomach and that sympathetic stimulation causes inhibition. It appears, then, that the fluid coming from the stimulated organ reproduces the characteristic effects of the vagus or sympathetic on different tissues, though whether every detail of the nervous effect is copied by the fluid remains an open question. The nature of the "vagus substance" is uncertain. Cholin has been suggested but does not quite meet the case. Brinkman and van Dam find that the fluid containing the "vagus substance" has a lowered surface tension and that the tension is restored to normal by the "sympathetic substance."

If these results come to be generally accepted we shall have a new and extremely interesting picture of the action of the autonomic system. The difficulty is that the effects seem to be capricious and are not easily reproduced. Some observers have failed to satisfy themselves that they occur at all outside the margins of experimental error. In view of this uncertainty we can only wait until there is a more general agreement as to the experimental basis of the humoral theory. If it is correct, the explanation of peripheral inhibition resolves itself into that of (*a*) the secretory mechanism which produces the inhibiting substance whenever impulses pass along certain fibres to the muscle, and (*b*) the way in which an inhibiting substance, adrenalin for instance, exerts its effect on the muscle fibre. Neither problem is new to physiology and it cannot be said that either is near its solution, but to have advanced thus far would be an important achievement.

The Gaskell effect.—Apart from the humoral hypothesis, but having some relation to it, is the rehabilitation of Gaskell's account of the electro-positive variation produced by the vagus. Gaskell showed many

years ago that in the quiescent auricle of the tortoise stimulation of the vagus increases the demarcation current between an intact and a damaged part of the muscle [13]. Since the wave of contraction is accompanied by a reduction in the demarcation current, the vagus seems to produce a state of affairs which is the opposite of the state of excitation. Considerable doubt was thrown on these observations by Einthoven [8], who considered that the change was due to a spread of the electrical effects produced by the vagus in the lungs, but Samojloff [26] has recently repeated the experiment with every precaution and concludes that the vagus does bring about a real change in the demarcation current of the heart. The change comes on slowly and persists for a short time after the vagal stimulation has ceased. It appears to be a steady condition and the records show no sign of fluctuations corresponding to the frequency of stimulation of the vagus. Meek and Eyster [24] had previously reported the same result.

A change of this nature might well be due to an altered permeability of the surface membranes to certain ions and this might be caused by a "vagus substance" secreted within or near the cardiac muscle. The important point is that it shows that the effect of the vagus is not confined to modifying the periods of activity; there is also a continuous influence on the heart muscle whether it is active or not. It is true that the increased demarcation current seems to persist for a longer period than the actual inhibition, so that it is conceivable that we are dealing with two distinct processes. But if the inhibition really depends on a definite alteration in the state of the heart muscle, it becomes very difficult to trace any connection between vagal inhibition and inhibition of the Wedensky type, where the inactivity is due to the non-arrival of impulses and the muscle is merely left unexcited. Even without the Gaskell effect it is difficult to see how an interference of the vagal impulses with one another or with the excitatory process in the heart could account for such effects of vagal stimulation as the shortening of the refractory period of the heart muscle; with the Gaskell effect in addition, the probability that vagal inhibition can be explained in this way becomes, for the present, negligibly small.

Various attempts have been made to investigate the nature and frequency of the stimuli which cause the vagus to inhibit the heart. However, the interpretation of such observations has always been handicapped by the fact that the stimuli take effect on pre-ganglionic fibres and that we do not know what relation the stream of impulses in the post-ganglionic fibre bears to that in the pre-ganglionic. The

point is emphasized by a recent paper by Querido [25] dealing with the conduction of impulses through the synapses of the superior cervical ganglion. The results are important, not only in connection with the working of the autonomic system but because the effects due to the synapse and nerve cell seem to be closely related to the effects of conduction through the grey matter in a simple reflex arc. Briefly, conduction through the ganglion converts a train of impulses of low frequency in the pre-ganglionic fibre into one of higher frequency in the post-ganglionic, and the ganglion also acts as a filter and prevents impulses reaching the post-ganglionic fibres at too high a frequency for effective conduction to the effector organ. In other words, wide variations in the frequency of pre-ganglionic stimulation produce much smaller changes (or possibly no change at all) in the frequency of impulses in the post-ganglionic fibres; thus we cannot be certain of what reaches the heart muscle when the preganglionic fibres of the vagus are stimulated at a given frequency or for a given time.

Inhibition in the claw muscles of astacus.—Before we pass to central inhibition there is another case of peripheral inhibition which should be mentioned, if only for the unusual nervous organization which it reveals. This is the inhibition of the claw muscles of astacus, the freshwater crayfish. The whole structure of the arthropods is so unlike that of the vertebrates that it is not surprising to find great differences on the functional side also, and this is revealed most strikingly in the control of the limb musculature. Whereas the skeletal muscle of a vertebrate is innervated by many thousand nerve fibres all of which are excitatory, the abductor of the crayfish claw is supplied by two nerve fibres only [23], one of them excitatory and the other inhibitory. The existence of a peripheral inhibitory mechanism is clearly related to the fact that the muscles can enter into a tonic contraction of peripheral origin. A persistent contraction of the abductor or adductor may develop spontaneously after the claw is removed from the body, or may be induced by electrical stimulation. Thus the isolated muscle might be either in the contracted or relaxed state, and evidently if the central nervous system is to be in full control it must be able to influence the muscle in either direction, to contract it if relaxed and to relax it if contracted.

The existence of a special inhibitory nerve-fibre was long suspected and was finally demonstrated by Hoffmann [15]. In the abductor the two main nerve-fibres branch repeatedly and a branch from each finds its way to every fibre of the muscle. Hoffmann finds that in the

proximal segments of the limb the two fibres run at a little distance from one another, and there one or other can be divided and the intact fibre stimulated. One fibre is clearly excitatory; if stimulation produces any effect, that effect is always contraction. Stimulation of the other has no effect if the muscle is relaxed, but produces inhibition if there is a tonic contraction. We know very little about the nature of the inhibitory effect. From observations on the claw muscles of the crab [9] it appears that the tonically contracting muscle is the seat of rhythmic electrical oscillations, so that we may perhaps liken the tonic muscle to the beating heart and the inhibitory nerve to the vagus. If the analogy holds good, the main difference lies in the fact that the successive "beats" of the crayfish muscle can fuse to give a smooth contraction, and that the automatic activity of the muscle is not so well developed as it is in the heart. The tonic contraction may appear without any obvious stimulus, but often a fairly lengthy period of stimulation is needed to start it, and as a rule the contraction does not return after a period of inhibition.

In the abductor muscle of the claw there is no indication of the separate mechanism for the twitch and the tonic contraction which is often found in invertebrates. If there were, we should have to credit the single excitatory nerve-fibre with a double function. It is no doubt rarely necessary for the animal to hold its claw open for long periods against resistance. In the adductor or closing muscle, on the other hand, the need for powerful, sustained contractions is obvious, and here we find distinct evidence of a dual system. Keith Lucas [16] showed that the nerve supply to the adductor was made up of two components of different excitability and different refractory periods, and that the muscle showed two forms of contraction according to the particular component stimulated, one a rapid twitch and the other much slower both in ascent and decline. Lucas's work on this problem was cut short by the war, and he had no opportunity of correlating these results with the histological evidence. It is therefore of great interest to find that, according to Hoffmann, the nerve-supply of the adductor is composed not of the single excitatory and single inhibitory fibre but of three and sometimes four fibres. One of these seems to be inhibitory and it needs little credulity to connect the other two (or three) with the slow and fast components found by Lucas. Further work is needed before we can be sure whether the persistent tonic contraction is due to the rhythmic activity of the slow component or to a steady state involving no loss of energy, but the rhythmic electric response of the crab muscle makes the former alternative the more likely.

Hoffmann's work reveals also a peculiar form of reflex co-ordination in astacus. If the tail is pinched, the claws are extended and opened. This reflex fatigues rapidly if the stimulus is repeated, but if the inhibitory nerve-fibre is cut through, all evidence of fatigue disappears and the response follows the stimulus with mechanical regularity. It seems, then, that the reflex is normally suppressed after a short time because the inhibitory fibres are brought into play and inhibitory impulses travel alongside the excitatory impulses to the periphery and annul their effects on the muscle. This seems a cumbersome method of securing a variety of response from the organism and gives us a picture of reflex fatigue unlike anything occurring in the vertebrate central nervous system.

The innervation of an entire muscle by a single excitatory nerve-fibre raises several points in regard to the gradation of contraction in the muscle. From Lucas's records it appears that the twitch shows little or no gradation according to the strength of the stimulus, but Hoffmann finds that when several impulses follow one another gradation may occur owing to changes in frequency, synaptic fatigue, &c. This and many other points in the nervous organization of the arthropods remain to be worked out in detail, but how far the results can be applied to the vertebrate nervous system is another matter. The two groups seem to have pursued such very different lines of evolution that the mechanism of inhibition in astacus may turn out to be quite different from any kind of inhibition in the vertebrate.

Central Inhibition in Vertebrates.

Inhibition as a discontinuous process.—It will be as well at the outset to recognize that the phenomena we group together as examples of inhibition occurring within the vertebrate central nervous system may not all be of the same type. For instance, the inhibitory effect of the brain-stem on the spinal reflexes may well depend on processes entirely different from those concerned in the reciprocal inhibition of an antagonistic muscle during a simple reflex. Most of our data relate to this latter type and the present discussion is confined to it.

Sherrington's work on reflex inhibition is well known, but it is so fundamental that we may be pardoned for insisting on some of its main conclusions. In the first place, he has pointed out that it is due to a cutting off of excitatory impulses from the motor neurones. The whereabouts of the block can be located because (*a*) the inhibition causes no change in the motor neurone itself or in the muscle, but merely

inactivity due to absence of stimulation; and (*b*) the failure takes place somewhere on the efferent side of the spinal mechanism, for inhibition cuts short an activity of central origin (e.g., an after-discharge) and does not merely check the flow of impulses entering by the sensory nerves. The other main conclusion is that the inhibition of antagonistic muscles forms part of the same reflex response as the contraction of the muscles which carry out the movement. The receptive fields for inhibition of the one set and excitation of the other are identical, the thresholds with various forms of stimulation are the same and the two processes begin and end at the same moment. The simplest explanation of this exact correspondence is to suppose that excitation of one and the same set of fibres in the sensory nerve produces inhibition of the one muscle group and contraction of the other owing to differences in the constitution of the synapses and conducting paths in the central nervous system. This explanation is embodied in Sherrington's well-known diagram.

Now so far as we know the stimulus to a sense organ produces a reflex by setting up nerve impulses of the same kind as those set up by an electric shock in an isolated nerve trunk. An important feature of such impulses is that they cannot become fused with one another into a continuous state of excitation. Until recently there was no direct proof that the natural sensory impulse resembled the artificial, but it has now been supplied by Forbes, Campbell and Williams [10], who have been able to record the electric response which accompanies the sensory (proprioceptor) impulse evoked by the sudden stretching of a muscle. In any case we know that the motor discharge consists of a series of such impulses from the motor centre, the frequency of the discharge often bearing some relation to that of the stimulus. But reflex inhibition usually appears as a perfectly steady condition even with a low frequency of stimulation, and this raises the question whether we may not be dealing with a central mechanism of quite different order which does not work by discontinuous impulses. Lately, however, two different lines of work have combined to show that under certain conditions reflex inhibition is not a steady state but passes rapidly through alternating phases of maximum and minimum effect with a rhythm as definite as that of the motor discharge and as closely related to the rhythm of stimulation. Brücke [6] devised the ingenious method of using two trains of stimuli having a slightly different frequency (50 and 51 a second), so that the moments of application of the stimuli in the two series coincide at first and then become more

and more out of phase with one another till the stimuli of the one series alternate with those of the other at intervals of 1/100 second, the phase difference then becomes smaller again until the stimuli coincide, the whole cycle lasting a second. One train of stimuli is arranged to evoke a crossed extension reflex and the other to inhibit it. If the strength is adjusted so that only a partial inhibition takes place, Brücke finds that the contraction waxes and wanes rhythmically every second, showing that the inhibition is greatest when there is a definite phase relation between the exciting and the inhibiting stimulus. The inhibitory effect of each stimulus must dwindle very rapidly, for a change of 1/100 second in the time of incidence of the exciting stimulus is enough to make the inhibition much less effective.

The same conclusion follows from Beritoff's [3] work on the electric response of a partially inhibited muscle. The semitendinosus is made to contract reflexly by a rapid series of stimuli (200 a second) to the

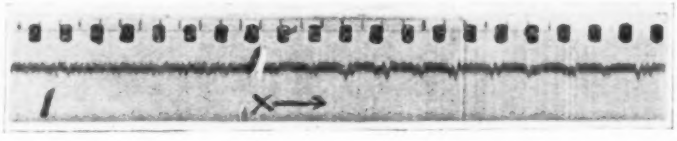

FIG. 1.—Electric response of quadriceps (decerebrate cat). At the point marked X the crossed extension reflex is partially inhibited by stimulating the ipsilateral popliteal at a frequency of 23 a second. The result is a series of short pauses with the same frequency as that of the inhibiting stimulus.

ipsilateral peroneal and the muscle gives a regular series of action currents at the same frequency. It is then partially inhibited by a slower series of stimuli (e.g., 25 a second) to the contralateral sciatic and the action current record now shows a series of gaps occurring every 1/25 second with one or two action currents missed out at each gap. Fig. 1 shows a record of much the same kind from one of my own experiments which amply confirm those of Beritoff. Under certain conditions, therefore, the inhibitory effect consists of a rapid succession of short pauses. From an analysis of many such experiments Beritoff concludes that the duration of the inhibitory effect of each stimulus may be as short as ·004 second. When stronger stimuli are used, however, the duration of each pause is longer and it may become so long that the successive pauses fuse into continuous inactivity and the inhibition is complete.

Continuous inhibition with strong stimuli.—Some idea of the processes at work when strong stimuli are used may be gained by

comparing the excitatory with the inhibitory effect. A common effect of an increase in the stimulus is the development of an after-discharge, an outflow of motor impulses from the cord lasting for some time after the sensory inflow has ceased, and this after discharge is accompanied by a corresponding period of inhibition in the antagonistic muscles. But the after discharge is not necessarily a terminal event: if the interval between consecutive stimuli is long enough, each stimulus of a series may produce its own after discharge and the electric response of the muscle will consist of a series of large primary waves at the same frequency as the stimuli, separated by groups of irregular secondary waves (fig. 2). It is unlikely that the after discharge is generated in the motor neurone, for Liddell and Sherrington [18] have shown this to be more or less aperiodic, the "momentum" of the response depending on the nature of the arc which leads up to the motor centre

FIG. 2.—Tibialis anticus (decerebrate preparation). Flexion reflex produced by stimuli at 23 a second to the ipsilateral popliteal. Stimuli 2·5 times threshold strength (5 units). The record shows primary and secondary waves and terminal after-discharge. Time marker (vertical lines at the top of the strip) gives 0·02 second intervals in all records.

and not on the motor centre itself. Thus each single stimulus may, if strong enough, produce some kind of sustained central activity which leads to a repeated discharge of impulses from the one motor centre, just as it produces a lengthy period of inhibition in the other. The general agreement in the duration of the motor discharge and the inhibitory pause can be shown very clearly by making simultaneous records of the electric response of two antagonistic muscles during reflex excitation and inhibition. Records of this kind are given in figs. 3 and 4. They show the electric response of an extensor (quadriceps) and flexor of the thigh (semitendinosus) in a decerebrate cat. By stimulating the popliteal nerve of the other leg at a frequency of about 200 a second the quadriceps is made to contract in a crossed extension reflex, the electric responses following one another without appreciable pauses at the same frequency as the stimuli. If the decerebrate rigidity is well developed there is no need to augment the extension by artificial stimulation; the electric responses of the quadriceps are less regular, but they are close enough together to show the inhibitory pauses. During the

period of extension the ipsilateral popliteal is stimulated at a lower frequency (23 a second), so that the flexors contract and the extensors are inhibited. When very weak stimuli are used there is little evidence of repetitive discharge in the flexors, and in agreement with this the inhibition of the extensor is not complete and consists of a series of

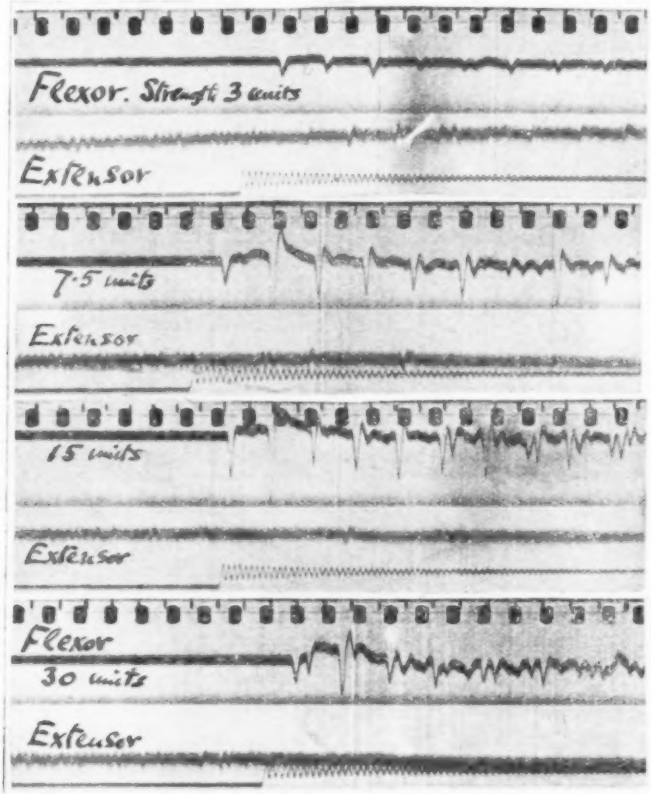

FIG. 3.—Simultaneous records of quadriceps (extensor) and semitendinosus (flexor) during inhibition of extension by stimuli at 23 a second. As the strength of the stimulus is increased the inhibitory pauses increase in length and secondary waves become more prominent in the response of the flexor.

short pauses synchronizing with the activity of the flexors. With stronger stimuli the periods of activity in the flexor and of inhibition in the extensor are both prolonged, and eventually a strength is reached at which the inhibitory pauses fuse with one another and the extensor is completely relaxed.

With this particular reflex preparation the inhibitory pause is rarely shorter and often somewhat longer than the corresponding motor discharge, so that inhibition may be complete in the extensor although the response of the flexors still shows periodic intermissions. Indeed, in some experiments where the flexion response is not well developed there may be continuous inhibition with little or no sign of repetitive motor discharge (fig. 4). In spite of these discrepancies, there is enough general agreement between the periods of inhibition and excita-

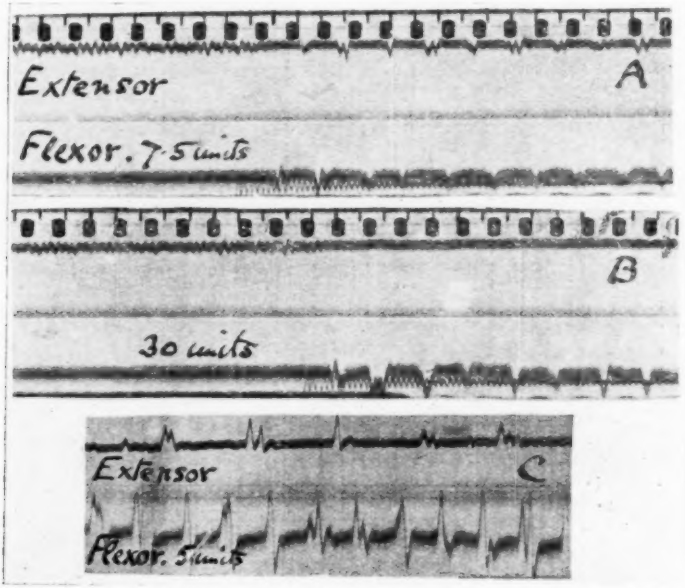

FIG. 4.—A and B, inhibition of extension in a preparation giving a poor flexion reflex. Inhibition is complete in B, though flexor responses are not continuous. C, ditto, another preparation.

tion under varying conditions to support the belief that both depend on a central process of the same kind. Both for excitation and inhibition we may say that there is a central process which is called into being by each impulse (or, strictly speaking, by each volley of impulses) in the afferent nerve, and the duration of these processes varies with the strength of the stimulus, i.e., with the magnitude of the afferent volley. At its briefest, the excitatory process gives rise to the discharge of a single impulse from each motor neurone, and the inhibitory process to a pause of ·004 second or less in the discharge of the antagonistic

centre. With stronger stimuli the central processes increase in duration, and each afferent impulse may now produce a whole series of motor impulses and a long period of inhibition. The facts so far discussed may be conveniently summarized by the diagram in fig. 5. No assumptions are made as to the nature of the "central processes," and, indeed, the diagram does not tell us much which is new, save that it emphasizes the short duration of the inhibitory effect.

If we try to advance farther, our explanations become more speculative, but it is worth while to discuss the various possibilities. There is, first of all, the nature of the central process or processes, which can convert a single afferent volley into a repeated motor discharge. According to an ingenious suggestion made by Forbes [11], there is no need to postulate a special kind of central activity at all, for the multiplication of impulses might result from conduction through branching pathways of different length. A single impulse entering a system of

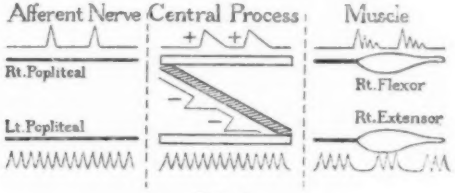

FIG. 5.

this kind would set up impulses in each branch and, owing to differences in conduction time, the impulses might be spread out into a long series as they converged again to a common destination. This hypothesis has much in its favour; the histological structure is there, and the stimulus which produces a repetitive motor discharge will generally give evidence of affecting a much wider area of grey matter than one that gives a single volley. At the same time it does not seem at all unlikely that certain regions of the grey matter may have the power of responding rhythmically, like a beating heart, for some time after a stimulus has reached them, or of remaining continuously in the excited state for a much longer time than the medullated nerve fibre. For all we know, these, and no doubt other factors as well, may all contribute to produce the repetitive discharge, and for the present we must be content to leave its central origin uncertain.

The mechanism of inhibition.—If we turn to the central process which accounts for the inhibitory pause, the most important fact is that

the pause may be extremely short and that it synchronizes almost exactly with the discharge from the antagonistic motor neurone. This suggests that the inhibitory pause is due to the arrival at some specialized part of the arc of an impulse or series of impulses of the same type as those which produce the motor discharge and set up by the same type of central process. It is conceivable that each impulse on arriving at a particular set of synapses might liberate a specific inhibiting substance which would block the other paths to the motor centre. The production of such a substance would have to be extremely rapid and its action extremely evanescent, but so, indeed, are all the physical and chemical changes associated with the nervous impulse, and it must be admitted that there is no insuperable objection to the hypothesis on this score. There is, however, another possibility which has, at least, the advantage of being more definite, although it seems to involve the view that central and peripheral inhibition are distinct processes. Though we have no knowledge of a specific inhibiting substance which might be set free by an impulse at the synapse, we are perfectly familiar with the depression of function which follows in the wake of one in a nerve fibre, the depression which causes the refractory period and the gradual recovery following it. It is not difficult to build up a scheme which would account for the inhibition as a consequence of the refractory state left by the inhibiting impulse. If the conducting paths in the central nervous system are anything like the peripheral nerve fibre, the path travelled by an impulse towards the motor centre would certainly be left more or less unfit for the conduction of other impulses as long as recovery was incomplete. The unfitness would not be communicated to neighbouring paths, for the refractory state is only left where the impulse has been; hence, if this state is to be the basis of inhibition, the impulse which inhibits must travel for part of its course in the same path as the impulses which excite. The path must be so constituted that the exciting impulses can pass through it successfully, provided that there is a sufficient interval between them to allow for recovery, whereas the inhibiting impulse cannot do so under any circumstances. This state of affairs might be realized by the arrangement represented in fig. 6, where A is the excitatory and B the inhibitory path converging on the motor neurone M, the shaded areas conducting with a decrement and uniting some little distance before M. By making the decremental path from B to M longer than that from A, we can account for the fact that an impulse from B can never succeed in reaching M, whereas impulses from A can do so provided that the path is given time for com-

plete recovery between each impulse. With such an arrangement, an impulse from B, though not itself exciting M, would leave the common pathway in a refractory state, absolute or relative, which would hinder the passage of impulses from A for a time depending on the rate of recovery of the path and the extent of the decrement in it. A rapid succession of impulses from B would produce continuous inhibition by never giving time for the complete recovery of the common pathway.

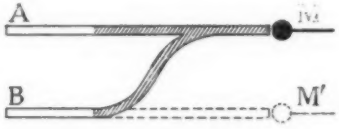

FIG. 6.

If the impulses from B also pass by a more direct route, dotted in the figure, to the antagonistic motor neurone M′, the periods of inhibition of M would synchronize with the discharge of motor impulses from M′, just as they do in the records shown in figs. 3 and 4. The diagram of reciprocal innervation given in fig. 5 is easily modified so as to include the present hypothesis, and the form which it now takes is shown in fig. 7.

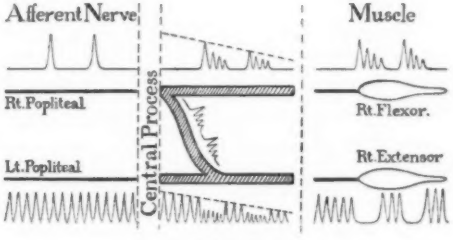

FIG. 7.

Explanations along these lines have been discussed briefly in Keith Lucas's monograph [17] and in this journal [1], and in greater detail by Forbes in his critical review of the whole subject [12], though at the time these accounts were written the evidence supplied by Brücke and Beritoff was still to come.[1] The suggested arrangement has the advantage of adhering closely to Sherrington's scheme, and it is unnecessary to assume that the central paths have properties radically

[1] Beritoff's earlier work (on the frog) was actually published in 1914, but like much of the literature of that year it passed more or less unnoticed until attention was called to it by his later work on mammals.

different from those of a peripheral nerve fibre. It leaves many phenomena unexplained, for instance those of post-inhibitory rebound. The inhibitory discharge from B to M seems to affect the subsequent activity of the central process at A in a way which is not immediately explained by the diagram, though the assumption of various side paths would no doubt give the requisite connection. The theory loses some of its appeal when we begin to multiply the side connections to account for each new group of phenomena, but it is true enough that the notion of single chains of neurones running an isolated course is a pure abstraction. Both Lutz's work [22] on sensory thresholds and Graham Brown's on motor rhythms [14] show that extensive central connections must exist so that the impulses arriving from the different fibres of the sensory root are pooled, as it were, in a common network and subjected to further synthesis and rearrangement before the result is finally handed on to the neurones of the motor centre. At the same time the evidence has steadily accumulated in favour of the view that the immediate cause of reciprocal inhibition is the refractory state left by the inhibiting impulses, and in one respect experiment has even verified a numerical prediction demanded by the theory [7]. It will be seen from fig. 5 that if the impulses from A to M are to reach their destination they must be spaced out so that the decremental region has time to recover between the passage of one impulse and the next. If we assume that a single impulse from B gives an inhibitory effect lasting for ·004 second, it follows that impulses from A alone will inhibit one another if they enter the decremental area at shorter intervals, ·004 second. Now a muscle which contracts on reflex stimulation does not become inhibited when the interval between successive stimuli is reduced to less than ·004 second. Therefore if the theory is correct the reflex arc must contain somewhere in the central area or on the motor side of it a region which will not allow excitatory impulses to pass through to the decremental area at intervals less than ·004 second apart, even though they arrive at shorter intervals from the afferent nerve. In agreement with this we find that the electric response of the muscle is, in fact, limited to a frequency of 250 to 300 a second (·004 to ·003 second between responses). Up to this limit the rhythm of the response follows more or less that of the stimulus, but with more rapid stimulation the responses become irregular but do not increase in frequency. We have good reason, then, for believing that the excitatory pathway is guarded against overcrowding in just such a way as the theory predicts. It would be a mistake, however, to attach too much significance to the

exact numerical agreement, for the figure of ·004 second for the duration of the shortest inhibitory pause is really not much more than an upper limit, nor is it universally allowed that the limiting frequency of reflex response does depend on the central paths rather than on the muscle itself.

If we compare the present theory, or some modification of it, with the view which supposes that inhibition is due to the production of a special substance which blocks the excitatory paths to the motor neurone, it will be seen that there is actually not very much difference between them. If an inhibiting substance is produced, its production must be almost instantaneous and it must disappear very rapidly; what the present theory assumes is that the "substance" is to be identified with the refractory state and that sustained inhibition is due to a series of refractory states and not to a steady production of an inhibiting substance. The main point at issue is whether the inhibitory pathway or synapse differs so radically from the excitatory that the impulses to the one liberate a special substance and those to the other do not. According to the present theory the difference is one of degree only and an inhibitory pathway might become an excitatory at any moment if its conductivity increased. It has therefore a distinct advantage over the notion of specially constituted arcs in explaining such effects as the strychnine reversal, the "set" of a particular arc in favour of inhibition or excitation and so forth. Evidence based on these and similar phenomena will no doubt soon decide whether the refractory period theory can give a really adequate account of central inhibition. If it succeeds we shall have a simple explanation of a small part of reflex co-ordination, but there is a great deal still untouched. As usual, the whole question of tone and its inhibition must be discreetly shelved until we can agree as to the nature of the tonic contraction in skeletal muscle. Apart from this it will be seen that some of the most important features of reflex conduction are relegated to an unknown "central process." So much of the character of the response must depend on the varying inertia and momentum of the central discharge [19], and so much of reflex co-ordination must take place at this level, that there can be little doubt that this is the main problem to be worked out before we can attempt to analyse the reflex into its constituent impulses.

REFERENCES.

[1] ADRIAN. *Brain*, 1918, **41**, 23.
[2] BARGER and DALE. *Journ. of Physiol.*, 1910, **41**, 54.
[3] BERITOFF. *Zeitschr. f. Biol.*, 1924, **80**, 171.

[4] Brinkman and van Dam. *Arch. f. d. ges. Physiol.*, 1922, **196,** 66.
[5] *Idem, idem. Journ. of Physiol.*, 1923, **57** 379.
[6] Brücke. *Zeitschr. f. Biol.*, 1922, **77,** 29.
[7] Cooper and Adrian. *Journ. of Physiol.*, 1914, **59,** 61.
[8] Einthoven and Rademaker. *Arch. f. d. ges. Physiol.*, 1916, **166,** 109.
[9] Ewald. *Arch. f. Anat. u. Physiol.*, 1911, 181.
[10] Forbes, Campbell and Williams. *Amer. Journ. of Physiol.*, 1924, **69,** 283.
[11] Forbes. *Physiol. Reviews*, 1922, **2,** 371.
[12] *Idem. Ibid.*, 1922, **2,** 361.
[13] Gaskell. *Journ. of Physiol.*, 1886, **7,** 451.
[14] Graham Brown. *Journ. of Physiol.*, 1914, **48,** 18.
[15] Hoffmann. *Zeitschr. f. Biol.*, 1914, **63,** 411.
[16] Keith Lucas. *Journ. of Physiol.*, 1917, **51,** 1.
[17] *Idem.* "The Conduction of the Nervous Impulse," Longmans, 1917.
[18] Liddell and Sherrington. *Proc. Roy. Soc.*, 1923, **95,** 335.
[19] *Idem.* Loc. cit., 407.
[20] Loewi. *Arch. f. d. ges. Physiol.*, 1921, **189,** 239.
[21] *Idem. Ibid.*, 1921, **193,** 201.
[22] Lutz. *Amer. Journ. of Physiol.*, 1918, **45,** 507.
[23] Mangold. *Zeitschr. f. allgm. Physiol.*, 1905, **5,** 135.
[24] Meek and Eyster. *Amer. Journ. of Physiol.*, 1912 **30,** 271.
[25] Querido. *Amer. Journ. of Physiol.*, 1924, **70,** 29.
[26] Samojloff. *Arch. f. d. ges. Physiol.*, 1923, **199,** 579.

ON THE PATHOLOGY OF ECHOGRAPHIA.

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In recent discussions on aphasia, the view has been expressed that the purely psychological aspect of the subject should be looked upon as of subsidiary importance and laid aside for the present until more pressing clinical and anatomical problems have been solved.

Some justification may be necessary therefore, if, in spite of this dictum, I take for my subject a rare condition in which the question of localization does not arise and discuss it in what may appear to be unnecessarily minute detail. This justification, I like to think, is found in the consideration that it is only in this way we can hope to obtain an insight into simpler and more usual processes; in this I am at one with W. James who said that "the great field of new discoveries is always the unclassified residuum."

At the International Congress held at Paris in 1900, I drew attention to an aphasic disturbance which, by analogy with echolalia, I called echographia [9]. The symptoms seemed to be unknown to others at that time, my French colleagues in particular accepting it as something quite new. In my paper, which was written from memory in Paris itself, I stated that Bateman [1] had seen something similar in a case of Voisin's in Paris. But this is not correct; Bateman, after describing Voisin's case of echolalia, mentions another case in which an aphasic patient echoed in writing everything that was said to her. Bateman explains this by assuming that the impressions on the auditory centre "stimulated" the writing centre.

The first case I described was that of an imbecile and almost illiterate peasant who whispered to himself during the writing tests "Don't do it," and who, when he could be persuaded to write at all, wrote down simple sentences like those a teacher dictates to his pupils in school, whilst written questions were copied but never answered. The second case was that of a man, aged 58, with right hemiplegia and typical sensory aphasia following ligature of the left carotid artery. He was word-deaf to a moderate degree, distinctly paraphasic and completely paragraphic; in writing tests he copied everything, even sentences containing remarks grossly derogatory to himself.

My interpretation in the first case was that the imbecile patient had never progressed much farther in learning to write than a stage when he was able to copy what his teacher had written, and that he therefore reacted in this way to writing placed before him. This interpretation finds support in an observation of Vinchon and Genil Perrin [16].

In the second case, I attributed the symptoms to an automatism showing itself in the writing of an unpractised individual and resulting from a dissolution of this power. As so often happens, after my paper was read similar cases of an earlier date came to light. Thus Bernard [2] reported a patient of Charcot's with motor aphasia who was chiefly remarkable from the fact that, when a written question was placed before him, he merely copied the question, holding the pencil in his left hand; at the same time it was obvious from his gestures that he understood the question but was unable to do more than copy it. In a note on p. 243, Ch. Féré (the editor of the second edition of Bernard's book) states that this symptom which he called "phonographie" was also observed in a hebephrenic patient in his ward. The name I have chosen is at the same time more correct and more comprehensive and should, I think, be retained. I might add here that Nadine Skwortzoff [15] also mentions this symptom.

Further, I should like to point out that something pertinent was reported in my own earlier writings. I pointed out, for example [10]: "If one places a written question before the patient, e.g., 'What is your name?' he takes the pencil and simply copies the question. It is noticed also that he draws the letters exactly as they are written; if a letter is written in an unusual way he takes pains to reproduce it exactly; the letter 'K' however is usually copied in his own handwriting, but on certain days, when his general condition is not so good, even this letter is drawn as it is written."

At a later date Marguliès [7] published two cases from my clinic with the object of exemplifying a guiding principle which I have often applied with good results, i.e., that for every disturbance caused by a gross lesion, similar disturbances of a purely functional nature will occur. This was true of his cases, as here the symptom was a transitory post-epileptic phenomenon.

In my first communication to the Paris Congress, however, and in my later papers as well, the symptom was described very briefly, and the same may be said of the report by Bernard and Féré, whilst Marguliès did not discuss it at all. I shall therefore proceed to make

the first serious attempt at an understanding of this very peculiar symptom, and shall base my remarks upon a new and remarkable case which has come under my observation.

On June 13, 1921, a Czech woman, aged 64, was admitted to hospital suffering from right hemiplegia and aphasia, following a stroke on March 8 of the same year; she was naturally placid, but during the days preceding the onset of the paralysis she became nervous and excitable. On the day of onset she was engaged in washing clothes, and her son, from whom the history was obtained, noticed that in wringing them she used the right hand awkwardly; also, that after carrying articles to the tub she placed them beside it instead of into it; her gait was swaying and unsteady; she made no answer to his questions, although she seemed to understand them; when put to bed she lay quietly and breathed deeply. On the following day she was taken to hospital, where, it is said, she ate nothing and did not recognize her friends. Whilst in hospital she improved rapidly and could soon walk without assistance. Eight weeks after the onset of her illness she began to say a few words, but with difficulty, e.g., "I want some bread" (in Czech this is one word); she repeated what was said to her and wept often; her son states definitely that she also asked for writing paper. (By this he meant, no doubt, that she expressed her wish to write by gestures.) She made signs of greeting to the physician on his morning round, and attempted to kiss his hand, an action which was often repeated later; she folded her hands as if in supplication, and spoke a few unintelligible syllables, which sounded like "Je . . . bud . . . no"; then she wept despairingly. No paralysis of the limbs could be detected; the forehead was more wrinkled on the right side than on the left; the abdominal reflexes were diminished on the right side. In response to questions she at once utters tearfully the fragments of words which, with slight variation, almost comprise her full vocabulary: "Ja (I) ne (not) bu (jargon), Ja le bu, Ja le bu . . ." "What is your name?" "Ja ne vim" (I don't know). "Zeman?" (her name). "Jo, jo" (Yes, yes). "Marie?" (her name is Frankiska). "Jo, jo." "How old are you?" She counts on her fingers and shows seven. "Have you a husband?" Shakes her head. "Have you any children?" Shakes her head at first, then indicates on her fingers: 2, 3 . . . 2, 3 (she has five children). "Where do you live?" (Jargon.) "In Zizkow?" "Jo, jo" (not true). "In which street?" (Jargon.) Several streets were mentioned, including the one in which she lives, but she gave no sign of recognition. "Can you write?" "I cannot," followed by jargon. When different objects are shown to her she repeats her jargon; occasionally one hears the words "Já nemužu mluvit" (I cannot speak), or "Nemužu mlivit" accompanied by gentle wailing over her disability. On further examination it becomes clear that she understands simple sentences. When asked to show her tongue she thrusts her chin forward, then opens her mouth and finally, after the order has been repeated several times, she points to her tongue. She knows her surname. When she sees the name Marie (this is not her Christian name) she accepts it at first, but then rejects it;

when invited to write her name she writes something in which some of the letters of her name are recognizable.

The result of the various tests for speech defects may be summarized as follows: Spontaneous speech—almost entirely jargon; "Vu la ji bu, a ja bul a bu," always accompanied by tearful gestures, and well modulated to indicate her feeling of impotence. *Repetition:* As a rule she refuses to repeat words, or talks jargon; sometimes she repeats a word or two correctly. *Recitation:* She repeats the Lord's Prayer, with folded hands, about half-way through quite correctly; sometimes she introduces jargon into the parts which she usually says best; the latter half is jargon; the rhythm and intonation are perfect throughout even in the jargon; once or twice she repeated the entire prayer without a mistake. In another prayer, which was not so well done, it was obvious that she was conscious of her defects; she said "Amen" at the end of it. She named some of the months correctly; when asked to name the days of the week she began correctly, but after "Wednesday" she said "May." She counted up to three, but could go no farther.

Naming objects.—Jargon.

Singing.—She continued the melody of a popular ditty in jargon, correctly at first but later out of tune.

Her understanding of spoken words was retained, words arousing emotion being best understood; for example questions regarding her deceased husband or her children, or the word "soldier" (her son is a soldier); further she recognizes the names of many objects if they are placed before her, or if she sees them represented in a book, although there is often delay in choosing the object named.

Writing.—As early as the second examination it was discovered that if she was asked to write with the finger she began to do so forthwith, and later on she made frequent attempts to write or carried out the movements of writing. Fragments of her name are all that she can write spontaneously; she is conscious of her errors and in trying to correct them she repeats them; she can write one or two figures correctly. The understanding of written words is almost entirely absent, but if the name of an object depicted in a book is written down she usually points to the corresponding picture; derogatory remarks produce no effect, but the sight of the word "soldier" makes her very angry (apparently because her son will not take her home). She is quite unable to read aloud. She copies single letters fairly well; some words are copied correctly, in others she makes mistakes, but she shows clearly by her expression that she is cognizant of them and tries to amend them.

It soon became obvious that she was absolutely incapable of *answering* anything in writing; she copied everything and this persisted; at first she copied words written in German, but a few days later she copied words written in Czech only and refused thereafter to copy words in any other tongue, even if they were written in capital letters. If the word before her was Czech she began to copy it at once, but if it was in a foreign language she hesitated, scrutinized the word closely, drew the paper nearer to her eyes, brushed it with

her hand, took it closer to the window, and did all those things that a person does who attempts to read an indistinct word. Whilst this was going on she mumbled to herself and her look seemed to say "I cannot understand this"; finally she shrugged her shoulders and in well-modulated jargon gave expression to her failure. Once or twice it happened that she gave the paper to a bystander, but it was not certain whether she merely gave it away or intended that it should be read to her. Now and then she wept or indicated in some other way that she was annoyed by the tests.

If foreign words were altered in appearance by the addition or interpolation of certain letters, or by appending accents or other marks so that they came to resemble Czech words, she copied them promptly.

After numerous repetitions of these tests an interval of more than two months was allowed to elapse.

FIG. 1.

At the beginning of September she had a convulsive attack. A few days later further tests were made with the following results: The aphasia is much the same as before; the "Ja la bu" persists and this is all she can say; copying is slower; she still scrutinizes foreign words as before but does not reject them so promptly, and it is easier to induce her to copy them by deception; meaningless words which look Czech such as "Kniduchzi" she rejects at first but later she copies them; when a series of letters is placed before her she inspects it carefully, gazes around, looks at it again and finally refuses to copy it. When asked to write down the name of objects presented to her she succeeds in isolated cases, for example she wrote "spectacles" correctly. During these investigations it was discovered that her bad handwriting was caused by a slight contracture of the right hand which prevented her from holding the pen firmly.

During the night of September 30 she died unexpectedly, the cause of death as we found at the autopsy being rupture of the heart.

The naked-eye appearances in the brain were (fig. 1) an area of softening in the left hemisphere extending superficially over the foot of the first frontal gyrus, the opercular portion of the pre-rolandic and post-rolandic gyri, across the sylvian fissure to include the anterior three-fourths of the first temporal gyrus and the adjacent portion of the second temporal gyrus as well as the whole of the anterior temporal pole. Superficially the supramarginal and angular gyri were intact.

Frontal sections show that the softening in deeper parts was distributed as follows: (1) In the section at the anterior limit of the lesion the softening is seen to extend to within 4 mm. of the ventricle. (2) In a section through the precentral gyrus the softening extends to the outer half of the putamen. (3) In a frontal section through the post-central gyrus the softening in the temporal lobe reaches a point 8 mm. from the descending horn of the lateral ventricle which lies immediately behind the hindermost point of the lesion.

The supramarginal and angular gyri are intact throughout. Apart from the changes just described, the brain, including the right hemisphere, shows no other lesion.

The general clinical aspects of this case can be dismissed in a few words: It is clearly a case of total aphasia caused by a slowly progressive thrombosis of a portion of the sylvian artery. One remarkable feature is the apparent integrity of the angular and supramarginal gyri; the significance of this cannot be considered until it has been confirmed by microscopical examination, but this need not hinder us in our evaluation from a functional point of view of the particular symptom which concerns us here.

Let us see then, without reference to earlier explanations, what we can gather from the facts of this case, just as it was presented to us and as I have tried to describe it.

First of all I must mention a symptom which is not included amongst those already known, namely, that soon after the onset of the illness, which robbed her almost entirely of the power of speaking, the patient evinced a desire to express herself in writing. Something of the kind is familiar enough in other cases of sudden loss of speech, e.g., in hysterical mutism; but so far as I know it has not been encountered before in aphasia apart from hysteria, and it is hardly possible to decide with certainty how this symptom, which is usually accepted as of great importance in differential diagnosis, should have arisen in this case. It might be described provisionally by saying that in an exceptional case, analogous say with some cases of pseudo-bulbar palsy, a woman free

from hysteria and painfully aware of her speech defect, immediately attempts to express herself in writing.[1]

Now in our consideration of echographia, and in our attempt to understand it, two points must receive attention. On the one hand due weight must be given to the peculiar feature of the case before us, namely, that the symptom was confined to words written in the mother tongue ; on the other hand a start must be made from a study of all the echo-phenomena if a satisfactory and all-embracing interpretation is to be achieved. With regard to the latter we must first mention the cases in which echographia is merely one of many echo-symptoms. Examples of this are seen in the cases described by Hobohm [6]. In an intermediate position we may place cases where echolalia and echographia appear together, as in those I have described myself or have allowed others to report from my wards; and if this case be regarded in its earlier stages as one of echolalia, then we may look upon the echographia of this patient at a later stage as a further weakening of a mechanism —a "tendency" to imitation—which had previously shown itself in two forms.

An explanation is still wanting for the fact that in the great majority of cases presenting echo-symptoms echolalia alone is found. Perhaps if we knew the reason for this it might help us to understand the peculiar feature of this case, the "selective" echographia (Echographie "mit Auswahl") as it might be called. In a preceding paragraph we classified a series of cases according to the intensity or extent of the symptoms. Now, before proceeding farther, if misunderstanding is to be avoided, and because we shall have to refer to the subject again later, it must be stated that the disturbances we are studying, according to the generally accepted view, are release phenomena; hence the arrangement given above corresponds to the weakening of a process which at first led to a general release of all sorts of motor discharges. At the same time we must remember that the removal of inhibitions alone would not explain the unusual motor phenomena with which we are dealing without the aid of the theory of "attitude" (for which we are indebted in the main to American authors) and Bergson's theory of the "schème moteur." In the light of these we may say that there exists a kind of constant "awareness" (Bereitschaft) towards the

[1] Since this was written I have found something similar reported in a case of Pieron's (*Rev. Philos.*, 1921, ii, p. 116) where following a severe attack of typhus the patient presented symptoms of aphasia which had altered but little five months after their onset: "Il parle très difficilement et cherche à écrire parcequ'il s'énerve de ne pouvoir s'exprimer."

impulses which have been rendered free by release. I may here recall that J. McKeen Cattell [3], and with him many other psychologists, regard the motor reaction as an integral part of perception, a view which is in accord with current physiological thought. With regard to my interpretation of the echo-phenomena, particularly of echolalia, the following words of Cattell may be quoted: "If someone speaks to me I am ready to answer. The response is due to the mechanism of the nervous system as organized at birth and reorganized by experience."

That echolalia so often remains after the regression of the process which at first gave rise to general release and all sorts of echo-symptoms, and that echolalia is by far the commonest of these symptoms, is perhaps explained by the fact that mimicry of the spoken word plays a more important part in the development of speech than other forms of mimicry. Observations on school children, and by S. Exner upon himself, have a bearing on the point, for they seem to show that even in normal persons an appreciable tendency to echo-speech presists.

In learning to write also mimicry plays a not unimportant part, and I do not think I am going too far when I connect this circumstance with the occasional appearance of compulsory echographia. That it is seldom observed is comprehensible because on the one hand the acoustico-motor speech reflex which I have shown is a so-called conditional reflex of Pavlov [11] is acquired in earliest childhood and is therefore an extraordinarily stable mechanism; whereas, on the other hand, writing is learnt later and is not developed to anything like the same extent.

At first sight this argument would seem to indicate that the admittedly feeble mechanism of echographia—a mechanism of which in contrast to echolalia no trace can be found in adults—must stand *last* in the descending scale of echo-phenomena. It seems to me, however, that an important general deduction can now be made and one which explains this apparent contradiction. From the very beginning I have maintained that the release which gives rise to echolalia is to be sought in a circumscribed process confined to the temporal lobe. I base this opinion on the fact that in the majority of the cases there is a lesion in this lobe, and that in cases where other regions are damaged this lobe is almost always injured as well. In addition I may say that the conception of an inhibition of the acoustico-motor reflex by a local process in the acoustic area is in accord with current views on the anatomical relationships of reflexes and release in general.

This is in opposition to the opinion of certain writers that the

process which gives rise to the release is more diffuse. But my view I think is more easily reconciled with the apparently typical order in which the echo-symptoms occur. Of course this order could be explained on the assumption that diffusely arranged inhibitions are removed by an intensive process and that severe and widespread echo-symptoms arise in this way; but this would not account for an isolated or residual echographia, or explain why a feeble inherent tendency, like imitation of writing, should make its appearance as the release diminishes instead of the stronger acoustico-motor reflex. For these reasons, therefore, I repeat that the facts under discussion are more in favour of my view that the various echo-phenomena are each the results of failure of inherent mechanisms which are laid down in circumscribed areas. In support of this conception I may well adduce all that we have learned of circumscribed inhibition and release from the study of lesions of the corpus striatum where an anatomical arrangement of various circumscribed centres has been proved to exist, or whose existence may be deduced from the facts available.

Against this attempt to elucidate the symptom of echo-writing—one which is made with all the reserve that so obscure a subject demands—the objection might be made that the symptom was due to the fact that the patient for some inexplicable psychological reason simply wished to copy, and this objection might seem to be supported by the "selective" echographia in this case.

The patient's behaviour when confronted with words in the Czech language was against this explanation; on this behaviour we must make our decisions because it was the rule, and the exception, namely "selective" copying, must be explained later in the light of the former. Now it was very noticeable that as soon as she saw a Czech word she went ahead promptly at copying, without any other stimulus to write beyond the sight of written words; and this she did in such a way that all who saw it gained the impression that they were face to face with a mechanical process in which there was no suggestion of real intention or choice. We are not justified then in interpreting the apparently selective echo-writing as an act of volition, although the attitude of the patient towards foreign words might suggest this explanation; rather is it our task to bring this attitude into line with the views we have expressed on echographia in general. This, it seems to me, is not very difficult if we assume that the impulse to copy is excited by familiar impressions only, whereas foreign words do not supply a stimulus powerful enough to arouse this impulse.

A point in support of this explanation of an apparent selective echo is given by a case which I described long ago [11]. In this case echolalia was most marked in response to the patient's mother tongue (Czech), less to German and least of all to Italian, of which the patient had a superficial knowledge only; as recovery took place the echo was confined to Czech. To explain these symptoms I postulated a transmitting apparatus delicately adjusted to the receptive apparatus [12], and I correlated the effect of different languages upon it with the patient's greater or less facility in each tongue, and I think it is reasonable to explain the behaviour of our present patient towards different languages in the same way.

In making this analogy, however, we must remember that in the first instance we are dealing with a severe case of echolalia, and in the second with a much more "mitigated" form of echo than has ever been observed in the realm of echolalia.

But this cannot prevent us from explaining even this mitigated form by an interruption between the receiving and transmitting mechanisms, for these exist for writing also, and we may say that foreign words do not give rise to impulses in the transmitting apparatus or that they render the conduction more difficult. Special reference may well be made again to the analogy, apart from time relations, of our case where the patient copied German as well as Czech at first and later only Czech, and the case of apparent "selective" echolalia.

Two observations on the development of language are introduced here because they lend support to the views I have expressed. Jules Ronjat [13] relates of his bilingual son: "Au commencement toute langue autre que le français et l'allemand est non avenue. Louis se rend certainement compte que ce n'est ni du français ni de l'allemand et sent en même temps un langage articulé qui peut avoir un sens pour les initiés; mais si l'on dit quelque chose devant lui, il ne veut pas le répéter, disant frequemment que 'c'est pas joli,'" and not till he was forty-two months old could he be induced to do so.

For an even more pregnant example we are indebted to the linguist Grammont [5] on the development of language in his daughter. This child had a nurse who spoke French with an Italian accent; one month *after* the departure of this nurse, who was replaced by a woman from Languedoc, the child began to speak with an Italian accent which persisted until the age of three years. "A deux ans et demi encore," says the father (p. 80), "si elle entendait un mot italien ou un mot languedocien accentué sur la pénultième, *elle le répète comme par plaisir*,

sans que cela soit utile, et avec une intonation absolument irréprochable." It is obvious that this corresponds to the apparent selection in the echo-writing of our patient.

In Hobohm's case, to which I have referred before, the patient showed in many ways that she felt compelled to produce the echo. This case proves that even when a relatively long period elapses between stimulus and discharge it is still the compulsion arising from release which is active, and that this feeling of compulsion enters consciousness. A parallel to this case, where the symptoms appeared without any gross lesion of the brain, is provided in one of my cases of echolalia with a gross lesion of the temporal lobe; at first there was "massive" echolalia; later the patient echoed questions asked by the doctor but did not echo in conversation with his wife: the compulsion it would seem was only present in certain circumstances.

If we are justified in taking the history of our patient to indicate that there was a period of echolalia at first, then this along with the son's statement regarding attempts at writing allows us to conclude, as in the case just mentioned above, that the "mitigated" echo had evolved from a more intensive echo-phenomenon.

Special attention must be given to the fact that our patient could be so deceived by the addition to foreign words of Czech letters or signs that she reacted by copying just as if the words were really Czech. Here the first question is whether the impulse for reactions of the kind we are considering is initiated by the word-picture itself, or by the acoustico-motor element of the "inner word" whose existence can be inferred from the lip movements which accompany the attempt to read. It is difficult to decide between these two possibilities because it is not feasible in the circumstances to prevent the patient from mumbling as she reads. The bearing of the patient during these confusion tests certainly gave the impression that she was performing a voluntary action, and this at first sight seemed to support the notion that the echographia was indeed decided by the patient's own choice; but on closer consideration it is easy to see that in this case the explanation given above for "selective" echo-writing is also applicable. The signs which were added to the foreign words and the approximation of certain groups of letters acted as it were as an adjuvant to the reflex for as a rule Czech words called forth the latent pre-existing echo-reflex, whereas foreign words failed to do so. Corresponding with this we found that the ruse was immediately successful in some instances; in others we observed that which we interpreted as tentative attempts at choice made possible by the tardy reflex response.

Further support is lent to the explanation I have given here of this remarkable symptom of incomplete echographia by the fact that my conception of a combination of reflexes and voluntary processes is not without parallel in the more familiar forms of spoken echo; it will perhaps suffice if I point out that I have proved in a number of papers that the forms of echolalia which I have called "mitigated" are to be explained by a conflict between the compulsion to imitate and the breaking through of the power of voluntary speech which is recovering gradually.

Finally, it is not out of place to refer here to experiments made by L. M. Solomons and G. Stein [14], where, in studying normal motor automatisms, results similar to those of pathological echographia were obtained; if a person practised at making automatic movements on a piece of paper with a pencil held in the hand while he was reading, a definite tendency to write words was noticed, especially short words like "the," "in," "it," and this increased when the narrative became exciting. In another experiment an attempt was made to influence the writing by dictation, while the subject went on reading; by degrees attention could be diverted from the writing and finally words were written unconsciously.

In a case reported by K. Goldstein [4] a somewhat similar differentiated reaction was observed. The patient, who had partially recovered from a sensory aphasia, understood words better when he could see the corresponding object; he could repeat some words correctly but "remained silent when a series of meaningless syllables was spoken." "It seems," Goldstein adds, "as if he can only repeat words he understands" (loc. cit., p. 175); later on (loc. cit., p. 182), it is stated that the patient behaved "as if he were deaf" when he heard foreign words, and further (loc. cit., p. 187), that "he could be persuaded with difficulty to imitate noises, but would not repeat sounds which resembled parts of words . . . because he was aware of his defect and was annoyed when he realized that the sound he had perceived and could have reproduced was not a normal word; he chose to remain silent rather than utter a garbled word." I consider that the symptoms in this case are analogous with those of our own patient, and I maintain that the explanation I have given for the one applies equally well for the other.

In conclusion I should like to devote a few words to the consideration that some readers perhaps may not have found adequate reference in this discussion on the various echo-phenomena to their equivalents in

normal persons. These are not lacking, however, and I am indebted in particular to the monograph of G. E. Müller [8] for references to his own cases and others in the literature. "All the subjects of my experiments except . . . showed movements of the arms, hands and fingers, by means of which they copied the figures, in the air or on the table. The same tendency to copy the figures was seen in the experiments of Ebert and Meumann, *although this was expressly forbidden*" (italics by me). Müller also mentioned the occurrence of these imitative movements in the observations of Smith and Kuhlmann.

With regard to the fact that in this paper I have given an important part to this inherent infantile tendency to mimicry, I should like to refer to another point mentioned by Müller (loc. cit., p. 385), namely, that in various experiments in teaching by the motor method, copying of the figure presented to them by drawing with the finger on the table or in the air, played an important part in young children, but with increasing years it gave place to other aids.

REFERENCES.

[1] Bateman. "On Aphasia," 2nd edition, Norwich, 1890.
[2] Bernard. "De l'Aphasie," 2me édition, Paris, 1889, p. 117.
[3] Cattell, J. McK. "Essays Philosophical and Psychological in honour of Wm. James." 1908.
[4] Goldstein, K. *Journ. f. Psych. u. Neurol.*, 1906, **7**, 172.
[5] Grammont. "Mélanges linguist off. à Meillet," 1902.
[6] Hobohm. *Mitteil. a. d. Hamburg. Staatskrankenanst.*, 1909, **9**, 227.
[7] MargulièS. *Monatschr. f. Psychiat. u. Neurol.*, 1907, **22**, 479.
[8] Müller, G. E. "Zur Anal. d. Gedächtnistätigkeit und des Vorstellungsverlaufes," *Zeitschr. f. Psychol.*, 1911, Erganzungsband, **5**, 378.
[9] Pick. *Rev. Neurolog.*, 1900, **8**, 823.
[10] *Idem. Arch. f. Psychiatr.*, 1896, **28**, 34.
[11] *Idem. Fortschr. d. Psycholog.*, **4**.
[12] *Idem. Arch. f. Psychiatr.*, 1916, **56**, 810.
[13] Ronjat, J. "Le développement du langage observé chez un enfant bilingue," Paris, 1913.
[14] Solomons and Stein. *Psycholog. Rev.*, N.Y., 1896, **3**, 492.
[15] Swortzoff, N. "De la cécité et de la surdité des mots dans l'aphasie," Paris, 1881.
[16] Vinchon et Genil Perrin. Quoted by Delacroix. *Journ. de Psychol.*, 1921, **18**, 122.

OLIGODENDROGLIA AND ITS RELATION TO CLASSICAL NEUROGLIA.[1]

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Introduction.

In spite of untiring study of the central nervous system which has demonstrated the intricate morphology of neurones and neuroglia, a very numerous body of small cells (the third element of Cajal) continued to be refractory to staining methods. The nuclei of these cells were easily demonstrable, but the cytoplasm, if seen, appeared to be scanty and without expansions. The brilliant studies of Del Rio-Hortega show that these cells possess complicated expansions. By demonstrating their detailed structure, he was able to show that they fall into two groups, differing in form and function. One group, which he chose to denominate *microglia*, is of mesodermal origin, and the other, *oligodendroglia*, composing the more numerous portion of the cells, he believes to be of ectodermal origin.

Microglia, as an entity, was confirmed by Cajal, and its morphological characters by Collado [15], Metz and Spatz [32], Ganz [26], Bailey and Hiller [7], and Penfield [34, 35]. Oligodendroglia, however, has received no confirmation as yet, though accepted by several writers. This is probably due to two causes; first, the difficulty of staining this element, and second, the fact that Cajal, repeating the work of his disciple, was unable to stain these cells, and, although he confirmed microglia as a group, he cast considerable doubt upon the validity of Del Rio-Hortega's description of the remaining portion of the cells previously termed by Cajal the third element. As Cajal, the great master of neuro-histology, has himself so often pointed out, it is extremely dangerous to assign value to negative results.

Thanks to technical instruction from Dr. Del Rio-Hortega, and with the help of certain minor modifications in the original method, which will be described, it is possible for me to confirm fully the original description of oligodendroglia.

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History.

Our knowledge of the interstitial cells in the central nervous system has increased step by step with the progressive improvement of staining methods. The publication of Golgi's method in 1886 [27] provided a means for the more exact study of neuroglia. The method of Weigert, 1895 [39], served to demonstrate with greater clearness the fibrillar structure of neuroglia, but led to the belief on the part of many who used the method in a complete separation of neuroglia cell from fibre. There followed the methods of Da Fano [16], Alzheimer [5], Fieandt [25], and many others. But, in general, the employment of aniline stains and various solutions of Mallory's hæmatoxylin led to a belief in a neuroglia syncytium, first described by Held in 1903 [29]. In 1909 [30] the same author described a membrane said to be penetrable by ectodermal elements but impenetrable to mesodermal cells, a misconception due to the staining method. Various modifications in the use of Bielschowsky's silver oxide [8], the application of Achucarro's tannin silver method [2], and Cajal's formol-uranium method [9], as well as Golgi's method, caused those who used them to doubt the existence of a neuroglia syncytium. Cajal's gold-sublimate method 1913 [10] gave an almost complete picture of neuroglia and demonstrated the morphology of the protoplasmic neuroglia simultaneously with the fibrous neuroglia of the white matter. It became easy to see (Cajal [11]) that every neuroglia cell of either type possessed at leastone sucker process or vascular foot, and that there was no true union of neuroglial expansions and thus no true syncytium.

Although the gold-sublimate method threw much light on the two types of common neuroglia, it left almost unstained the protoplasm of the rest of the adventitial or non-nervous cells, a defect shared by all previous methods, except perhaps Robertson's platinum stain [36]. In 1918, Del Rio-Hortega [17] described a method of using silver carbonate to stain neuroglia and connective tissue. It soon became apparent that with modifications of this method he could show the rest of the interstitial cells, or the third element of Cajal, in a new light. These cells were found to possess complicated cytoplasmic expansions, and there followed rapidly Rio-Hortega's description of the two cellular groups, microglia [18] and oligodendroglia [21].

Thus there were added to the already recognized common neuroglia two new classes of non-nervous cells. The interstitial cells could now be divided into four chief classes: (1) fibrous neuroglia; (2) proto-

plasmic neuroglia[1]; (3) microglia; (4) oligodendroglia. The last two groups of cells have long been looked upon as an enigma and denominated in various fashions: neuroglia cells without expansions (Nissl), indifferent cells (Bonome), naked nuclei (Schaper), round cells (Eisath), pre-ameboid cells (Rosental), and adendritic corpuscles or third element (Cajal). Much of the diversity of opinion concerning these cells is doubtless due to the fact that these authors were often studying, as Rio-Hortega has demonstrated, two types of cells, not one.

For the sake of completeness and to facilitate comparison with oligodendroglia it is in order to describe very briefly *microglia*, although we have done so more completely elsewhere in other communications [34, 35]. These cells have the same general characteristics in the central nervous systems of all animals so far studied. The normal form in adult brains is found in greater numbers in the grey than in the white matter. The nucleus is small and often irregular or elongated in shape. It contains rather heavy chromatin elements (fig. 1, A). The cytoplasm passes out into expansions (figs. 6 and 8), so as to give the cell body frequently a bipolar or tripolar appearance. The expansions have numerous branches and terminal spines. In pathological conditions involving destruction of cerebral substance the expansions become shorter and thicker, producing *Stäbchenzellen*, cell forms first described by Nissl in general paralysis [33]. Further change transforms microglia into amœboid cells possessed of reticulated cytoplasm. In this form they become migratory phagocytes, cells long recognized and described under the name of *Gitterzellen*, "granulo-adipose cells," "scavenger cells," &c. Rio-Hortega has demonstrated microglia to be of mesodermal origin and no valid arguments have been brought forward to the contrary.[2] Microglia has therefore no relation to neuroglia, as the latter is of ectodermal origin.

[1] The fibrous and protoplasmic neuroglia have of course long been recognized. They have been called common neuroglia or macroglia (Cajal), to distinguish them from the newly described more asteroid elements. In this communication the term *classical* is used in place of common to make the same distinction. Both types of neuroglia possess vascular feet and comparatively large expansions. In the cytoplasm of both are to be seen gliosomes or large granules which have been taken to indicate that the cells are tiny glands of internal secretion (Nageotte, Mawas, Achucarro). Fibrous neuroglia is found almost exclusively in the white matter and contains the robust fibres of Ranvier-Weigert and few gliosomes, while the protoplasmic form is almost exclusively in the grey matter and possesses no such fibres but many gliosomes. Mixed forms are not infrequent, especially in certain animals (Cajal [11]), and present some expansions with fibres and others without fibres. There are, of course, neuroglia cells whose fibrous expansions ramify in a superficial "felting" beneath the pia, and those which form vascular satellites and whose prolongations weave a fibrous covering to vessels (Andriezen [6]).

[2] He would therefore call microglia the true third element of the central nervous system.

Cajal repeated some of the work of Rio-Hortega, using a "modification of the method of Bielschowsky" [13]. Under the name of "*mesoglia* of Robertson and Rio-Hortega," he verified fully the description of *microglia* given by Rio-Hortega and agreed to its mesodermal origin and transformation into *Gitterzellen*.

Considerable confusion has resulted from the recent use of the term "mesoglia," which was first employed by Robertson in 1900 [37]. The Scotch investigator employed the term to describe certain cells stained specifically by his platinum method [36]. He at no time published anything more than a brief descriptive note concerning these cells, but assumed them to be of mesodermal origin and hence called them mesoglia. After examining an original preparation of Robertson and comparing it with sections stained by Rio-Hortega's method, I am convinced that the mesoglia of Robertson and the oligodendroglia of Rio-Hortega are the same, as pointed out by the latter author. Microglia cells are not stained in Robertson's section. Preparations by both methods show cells which appear in rows in the white matter, are very numerous and provided with expansions similar in form and arrangement. Likewise the description and drawings provided by Robertson in his Textbook of Pathology[1] [38] correspond with the oligodendroglia of Del Rio-Hortega.

To Robertson, therefore, belongs the credit of the first description, incomplete though it was, of the protoplasmic expansions of oligodendroglia. Priority in the description of microglia belongs to Del Rio-Hortega, as well as the credit for having independently provided a complete differentiation of both groups of cells. Unfortunately, Cajal, as he admits, had never read the communication of Robertson but knew it only at second hand through a paper by Cerletti [14].

It seems best to drop the term mesoglia altogether as it leads only to confusion. If used at all it must be applied to microglia, which is of mesodermal origin, but this must then be clearly distinguished from the mesoglia of Robertson, which, corresponding to oligodendroglia, is apparently of ectodermal origin.

Unnecessary multiplication of scientific terms is a source of much confusion. Thus, Metz and Spatz [32], in an interesting confirmation of microglia, choose to apply to those cells the term *Hortegaschen Zellen*,

[1] After discussing the established epiblastic origin of classical neuroglia, Robertson says [38], "The fact that the other elements" (mesoglia) "are in reaction and form so sharply contrasted is at least strong presumptive evidence that they are of widely different nature and therefore mesoblastic in origin." He gives no grounds for their mesoblastic origin except the difference in appearance and stainability of these cells as contrasted with neuroglia

and Bailey and Hiller [7], in a comprehensive review of the work on the *interstitial tissues*, group microglia and oligodendroglia under the heading of mesoglia, thus assuming both to be of mesodermal origin. Gorriz [28] very recently refers to *mesoglia and derived cells* by which he apparently meant to designate microglia. The only full description of either cell group is that of Del Rio-Hortega who employed the non-committal but descriptive terms of microglia and oligodendroglia. It seems best to adhere to that terminology.

Technique.

That oligodendroglia is very difficult to stain completely has been well demonstrated by the history of these so-called *adendritic cells*. The platinum method of Robertson [36] was specific when successful, but it was so capricious that no one has been able to use it to elaborate the meagre description provided by the Scotch pathologist at that time.

A much more complete description has been provided by Del Rio-Hortega [21], using ammoniacal silver carbonate. Even by this method the results are variable. Some undetermined factors in the preparation of the tissues for the silver bath at times cause only microglia to be stained, or microglia and classical neuroglia. When the tissue is in a more favourable condition oligodendroglia is stained, but there is also impregnation, though incomplete, of the two above elements as well. When the tissue is in the most favourable condition a completely selective stain of oligodendroglia is obtained and the cell prolongations are beautifully clear-cut and appear much ramified.

Cajal employed a procedure [13] (under the name of "a modification of Bielschowsky's method") which differed in no essential respect from that of Del Rio-Hortega, except that he substituted the silver oxide of Bielschowsky for Del Rio-Hortega's silver carbonate solution. Cajal pointed out that in the ammoniacal silver carbonate of Del Rio-Hortega the active agent is probably oxide of ammoniacal silver, just as in Achucarro's tannin-silver method and the modification which he himself was employing. In the Achucarro and the Cajal methods Bielschowsky's silver oxide solution is used as an impregnating bath. Rio-Hortega's silver bath differs from that of Bielschowsky in that it is prepared by adding Na_2CO_3 or $LiCO_3$ to $AgNO_3$ instead of adding NaOH as in Bielschowsky's method. In both cases the precipitated silver salt is re-dissolved by the addition of ammonia. Thus, Bielschowsky's

solution contains the hydroxide of ammoniacal silver, while Del Rio-Hortega's solution contains carbonate of ammoniacal silver. Both of these may be considered to yield AgO.

Inasmuch as Cajal used the same general procedure as that previously employed by his disciple, the two methods should not be considered separately. As used by both investigators appropriate variations of these methods result in stains of neuroglia, connective tissue, Nissl's granules, &c. [17, 20, 28, 12], but Cajal states that, unlike Del Rio-Hortega, he was unable to make the microglia impregnation completely selective and could not impregnate oligodendroglia at all.

In brief, the method[1] employed by Del Rio-Hortega to stain oligodendroglia is as follows :—

(1) *Fixation.*—Fix twelve to forty-eight hours in Cajal's ammonium bromide-formalin solution.

(2) *Bromuration.*—Heat the block in fresh fixative in a small covered dish for ten minutes at a temperature of 45-50° C. Such heat is uncomfortably hot to the hand when applied to the dish steadily.

(3) *Section.*—Cut on a freezing microtome at 15 to 20 micra.

(4) *Wash.*—Wash twice in distilled water. Add ten to twenty drops of ammonia to the first water.

(5) *Impregnation.*—Silver bath. Sections to remain one to five minutes as determined by trial.

(6) *Wash.*—Distilled water. Agitate gently for fifteen seconds.

(7) *Reduction.*—Formalin 1 per cent. Do not agitate the section but allow it fall to the bottom. The colour change comes quickly.

(8) *Wash.*—Distilled water. Examine wet section on microscope.

[1] The dishes used for the liquids are of glass placed on white background. For washing water and for formalin, ordinary Petri dishes serve very well. For the solutions smaller glass dishes are economical and serve as well. Sections should be transferred with a small bent glass rod.

The solutions used are as follows :—

Cajal's *fixative*-formalin (Merck), 40 per cent. ..	14 c.c.
Ammonium bromide	2 grm.
Water	86 c.c.

Del Rio-Hortega's "*strong carbonate of silver*" is prepared as follows :—

Solution of silver nitrate (Merck), 10 per cent. ..	5 c.c.
Solution of sodium carbonate (*pure*), 5 per cent. ..	20 c.c.
Ammonium hydroxide (sufficient to dissolve precipitate.)	
Distilled water to	45 c.c.

The ammonium hydroxide, as indicated above, should be added drop by drop until the precipitate is just dissolved, stirring the solution all the while. Finally, filter and place in a dark bottle, where it will keep for long periods.

Stock formalin should be kept in a bottle over chalk to prevent excessive activity.

(9) *Toning*.[1]—Gold chloride (yellow, 1-500). Tone until sections are grey.

(10) *Fixation*.—Sodium hyposulphite (5 per cent.). Until sections are flexible. One minute is ample for this fixation.

(11) *Wash*.—Water.

(12) *Mount*.—Dehydrate and clear, using 95 per cent. alcohol followed by carbol-xylol-creosote mixture. Mount in Canada balsam.

In more difficult cases Del Rio-Hortega has recourse to certain expedients, among which are immersion of the sections in alcohol before the silver bath for a variable period up to twenty-four hours. Anhydrous sodium sulphite (about a 5 per cent. solution, prepared fresh) may be used in the same way. Another helpful expedient used by him is to pass the section through alcohol between the silver bath and the reducing formol. In what way these alteratives may act it is impossible to say.

More constant results were obtained by me, particularly when studying the central nervous system of rabbits, by using the method with alterations as follows :—

(1) *Fixation*.—Fix in (*a*) Cajal's ammonium bromide formalin solution two to twelve hours; followed by (*b*) thirty-six to forty-eight hours in 95 per cent. alcohol. Blocks should be about 3 mm. in thickness.

(2) *Wash*.—Wash blocks in running water at least four hours to remove alcohol.

(3) *Section*.—Cut on freezing microtome.

(4) *Wash*.—Wash sections. A few drops of ammonia may or may not be added.

(5) *Impregnation*.—Silver bath. Six to twelve sections to remain in bath fifteen minutes to two hours as determined by trial. The most favourable time to remove sections is when they are beginning to turn brown.

(6) *Reduction*.—Pass sections directly to formalin and agitate, as in Del Rio-Hortega's method for microglia.

Wash, tone, fix, dehydrate, clear, and mount as outlined above.[2]

[1] Toning, originally described by Cajal, consists in substituting gold for the silver. The section gains considerably in clearness, so that thicker sections may be used. However, if toning be omitted it is often easier to study the cytoplasm of the cell body. If the gold bath is not used, place sections in 10 per cent. formalin or pass through sodium hyposulphite before dehydrating, in order to secure permanent preparations.

[2] Thus it will be seen that the modification differs from Rio-Hortega's original method in the addition of alcohol as a mordant, the omission of bromuration, increase of time in silver, and agitation in the reducer.

With this alcohol mordant it will usually be found that reduction after one to three minutes in silver produces a particularly clear selective impregnation of microglia. In addition to oligodendroglia nerve fibres and nerve cells are often stained faintly, which enables one to study the relation of oligodendroglia satellites to these structures.

A different method was used to prepare the section from which fig. 9 was drawn. It gives a remarkably clear specific stain of gliosomes in the protoplasm of oligodendroglia as well as in common neuroglia. The method is a new one devised by Del Rio-Hortega and will be published by him shortly. This study was greatly aided by his generous permission to use it.

Structure of Oligodendroglia.

In the *white matter* may be seen, by means of practically all common stains, series of nuclei appearing often in pairs or closely set

Fig. 1.—Nissl stain of the cerebellum of a cat. **A**—microglia nuclei, **B**—oligodendroglia, and **C**—neuroglia nuclei.

rows parallel to surrounding nerve fibres. They are the nuclei of the "interfascicular glia" of Del Rio-Hortega, or "oligodendroglia" of the same author. These nuclei as seen, for example, by Nissl's stain are round or polygonal as though compressed by the closely packed medullary sheaths about them. They are slightly larger than the corresponding nuclei in the grey matter. The nuclear chromatin is less than that seen in microglia nuclei (compare A and B, fig. 1).

Included in a row of oligodendroglia nuclei may often be seen a larger nucleus, which is that of a fibrous neuroglia cell, or "intercalated" cell, and an occasional microglia nucleus may appear either in the series or beside it. From the neuroglia nucleus that of an oligodendroglia cell can be distinguished by its smaller size and larger amount

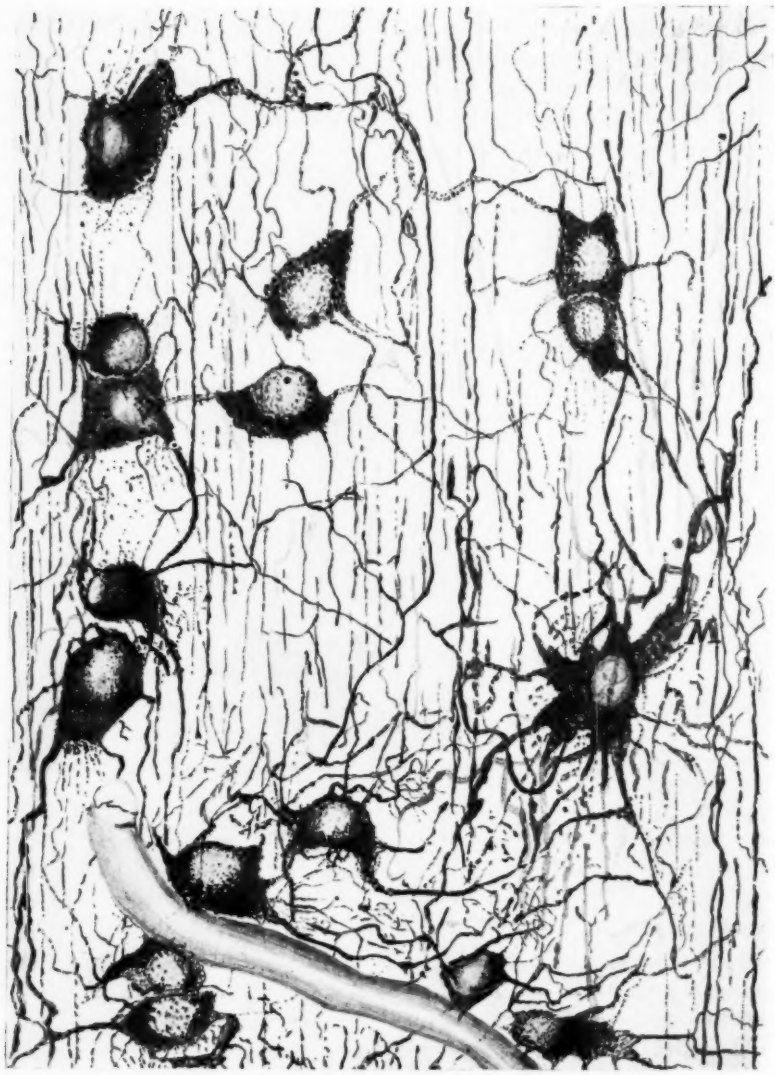

FIG. 2.—Oligodendroglia in the cerebellar white matter of a cat. The larger expansions run generally parallel to the nerve fibres. **M** is not a typical oligodendroglia cell but has characteristics of both oligodendroglia and classical neuroglia. All stains unless otherwise specified are made by the silver carbonate method modified for oligodendroglia.

of chromatin (compare B and C, fig. 1). From the microglia nucleus it can be distinguished by the facts that it appears round or a little oblong, and that it is usually a little larger and its chromatin granules are finer than those of microglia. On the other hand, microglia nuclei are usually irregular in shape and often elongated (A and B, fig. 1).

In a Nissl preparation the oligodendroglia cytoplasm is often faintly stained. It is usually disposed at one pole or the other of the

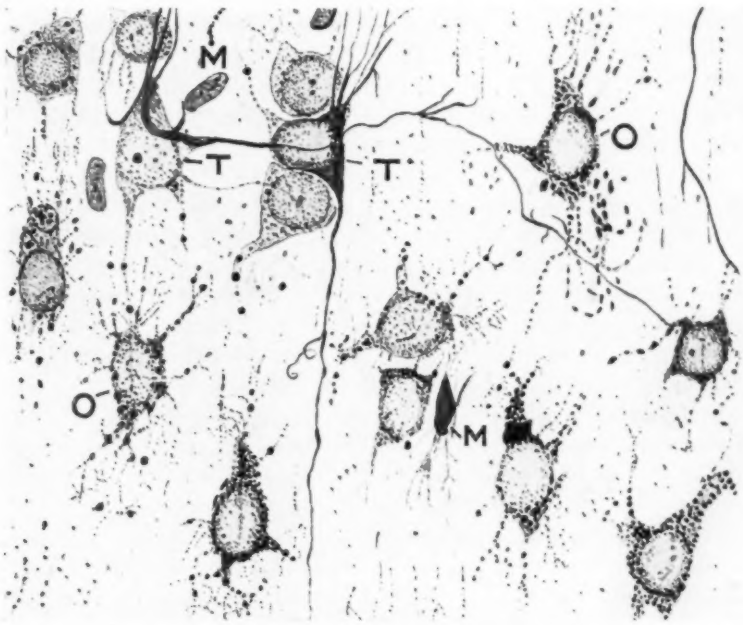

FIG. 3.—Cerebellar white matter of an eight-day kitten. Spongioblasts appear to have developed into young oligodendroglia (O), and immature neuroglia (T). The transitional forms (T) present neuroglia expansions on one side and immature or oligodendroglia-like expansions on the other. M—microglia nucleus.

nucleus and, as would be expected from the situation of the cell within the neuron cable system, it is displaced from the nucleus in the direction in which the " cables " pass.

As shown by silver carbonate, most of the cytoplasm lies at the base of the larger expansions (fig. 2). The cytoplasm contains no fibres but is often granular. In new-born animals at the time of most active myelinization these suggestive granules are particularly large (fig. 3).

They are seen not only in the cell body but also in the expansions. When a specific stain is used for granular components of the cytoplasm it is found that the cell body and prolongations contain many small granules or mitochondria, and larger round or oval granules (fig. 9), which are identical in appearance with the gliosomes stained in common neuroglia, a fact which will be discussed below.

Cajal demonstrated a well developed Golgi apparatus situated to one side of the nucleus where the larger amount of protoplasm was found, which would place the apparatus at the base of the largest expansion. This eccentric position within the cell is typical of the appearance seen in embryonal cells, as pointed out by Rio-Hortega, but also of that seen in gland cells where the Golgi apparatus tends to be placed in that side of the cell from which the cell secretion is discharged. That the cytoplasm contains two small centrioles was pointed out by Rio-Hortega [21].

Irregular stumps or short projections of cytoplasm have been frequently described in the third element, as shown for example by the formol-uranium method. A successful silver impregnation demonstrates the fact that these projections are in reality the bases of expansions of considerable length and complexity. The heavier expansions pass across surrounding neuron fibres or more often are parallel to them (fig. 2). In the more complete preparations it will be seen that these fibres give rise to flattened branches that form an incomplete envelope about the adjacent myelin sheaths (fig. 7). In sections which cut across the nerve fibres of the white matter at right angles the expansions of oligodendroglia are seen to be broad and short (fig. 4). These coarse expansions give rise to the longer and more slender branches which pass along with the nerve fibres and parallel to them (fig. 2). In fig. 4 it can be seen that small expansions encircle the nerve fibres which are stained, but there is always a clear zone between the expansion and nerve fibres. This zone corresponds to unstained myelin sheaths. Inasmuch as oligodendroglia fibres form an irregular and incomplete network about the myelin tubes of the central nervous system, they may be said to form a discontinuous sheath for the myelin in a manner analogous to the sheath of Schwann about peripheral myelinated fibres.

That these cells have a *function* in some way similar to the cells of the sheath of Schwann and to the subcapsular cells in the spinal ganglia was suggested by Cajal [11] before it was possible to stain the oligodendroglia expansions. Rio-Hortega [24] has now provided anatomical substantiation of such a view. That these cells have to do with the

formation and maintenance of the myelin sheath is borne out by the facts that: (*a*) They first appear in the new-born central nervous system at the time of maximum myelinization; (*b*) there is found in their cytoplasm and enveloping expansions granules which are especially large at the time of birth and which resemble the granules seen in the cells of secreting glands; and (*c*) they are very numerous, especially in the white matter, and the position and relation of their cytoplasmic expansions to the myelin sheaths is similar to the arrangement of the sheath of Schwann.

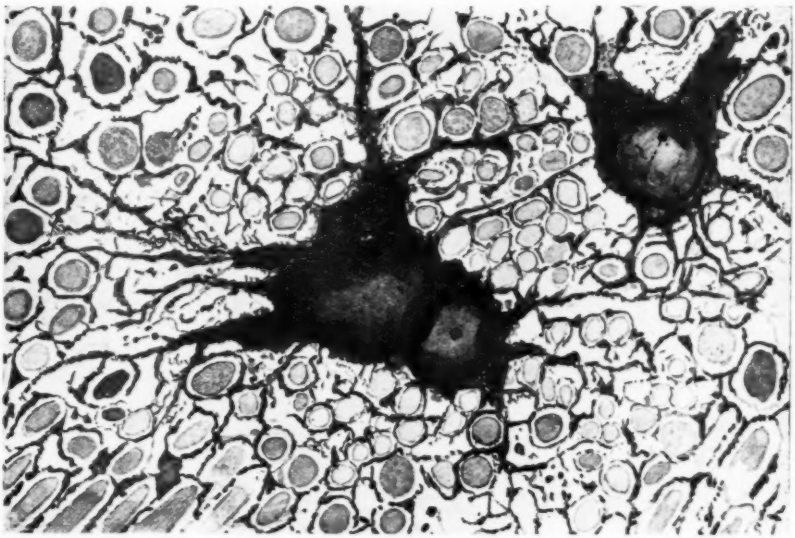

FIG. 4.—Cross section of nerve fibres in the cerebellar white matter of a rabbit. Three oligodendroglia cells, the small expansions of which tend to encircle the unstained myelin sheaths.

Oligodendroglia forms by far the most numerous group of cells in the central nervous system, after nerve cells. They must, therefore, perform a function of considerable importance and one which accounts for their presence, particularly among the myelin sheaths of the white matter.

In the *grey matter* oligodendroglia cells are found, though fewer in number. Here they are satellites for nerve cells, appearing most frequently about the neurons of medium size. It is a matter of frequent observation that satellite nuclei are very rare about the large

pyramidal cells of the motor area (Betz cells), and about the cells of Purkinje and the largest cells of the pons and medulla. Though oligodendroglia cells are not found applied to these neuron bodies, yet in the bulb at least they are found about the origin of the neuronal expansions of some large cells which have no satellites proper to the cell body.

Oligodendroglia of the grey matter seems to be smaller than in the white matter. Its expansions, as seen by the most successful impreg-

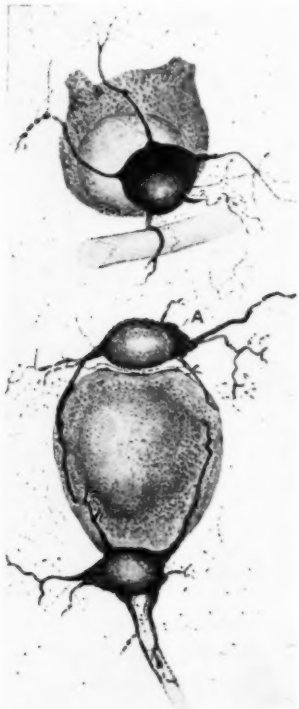

FIG. 5.—Oligodendroglia satellites about neurons from the cerebral cortex.

nations, are smaller than those of the "inter-fascicular glia." The cells are applied to the convexity of the neuron body (fig. 5), but a narrow intervening zone can often be seen (fig. 5A). Cajal observed that neuroglia expansions never pass between neuron and satellite, however profuse may be the ramifications of those expansions over the nerve cell. The oligodendroglia expansions pass over the surface of the nerve cell and usually end at a distance, though some expansions appear to pass only over the cell or cell and dendrite.

Perineuronal satellites have been the subject of considerable interest, especially in pathological conditions. But also under normal conditions it is well recognized that satellite cells surround neurons with the exception of the large specialized nerve cells mentioned above. Cajal [11] suggested that the relationship was a symbiotic one.

All perineuronal satellites are not oligodendroglia. A smaller proportion of them are microglia. These latter cells are applied to the surface of neurons in a manner similar to that of oligodendroglia, except that the nucleus and cytoplasm, being more irregular and plastic, wrap themselves more about the cells (fig. 6). The prolongations pass over the neuron body and end as usual in much ramified expansions about other structures. Frequently several oligodendroglia cells and a microglia cell are found applied to the same neuron.

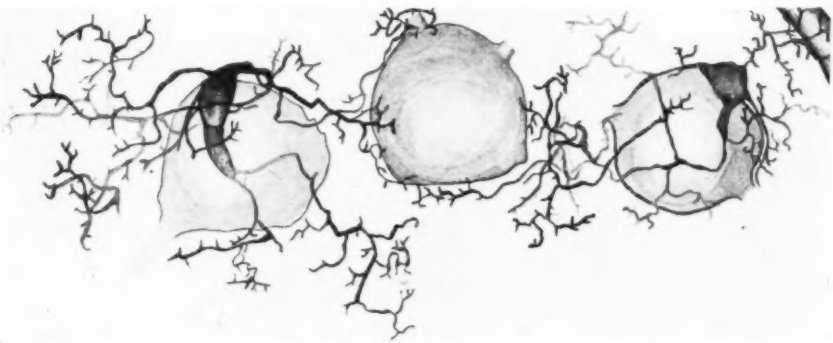

FIG. 6.—Microglia satellites about neurons from the cerebral cortex. The irregularity of microglia cell body and nucleus and the bushy expansions contrast typically with oligodendroglia figures.

In any process of "neuronophagia" (Marinesco [31]), phagocytosis is in all probability carried out by microglia, as Rio-Hortega suggested [21], for microglia very readily enters into phagocytic activity. Under pathological conditions,[1] microglia has been described in its transitional form to Stäbchenzellen applied to nerve cells (Nissl [33], Achucarro [1], Collado [15], *et al.*). Study of the much vexed question

[1] Marinesco [31] has noted that in pathological conditions some satellites present only a small nucleus and unstained cytoplasm which resembles a surrounding areola. Others present nuclei which are often irregular in shape and stained cytoplasm which tends to form expansions. Marinesco supposed all these cells to be neuroglia, but in view of the knowledge gained with Rio-Hortega's methods, one must assume that he was studying oligodendroglia and microglia, at least in part.

of neuronophagia by means of the methods provided by Del Rio-Hortega offers what is probably a fertile field of investigation.

Perivascular satellites, like perineuronal satellites, are of two types. Figs. 2 and 7 show oligodendroglia cells applied to the adventitia of small vessels. A few expansions in fig. 7 may be seen to ramify over the vessel, but for the most part the expansions pass out into the white matter to weave about the medullary tubes in a manner similar to that of the prolongations of those cells which are not in relation with vessels. There are no expansional terminations that suggest vascular feet.

The second type of cell found upon the small vessels of the central nervous system is microglia. Similarly to oligodendroglia, microglia cell bodies are applied closely to the blood-vessel. Their expansions pass out into the neighbouring tissue, often ramifying over nerve cells as indicated in fig. 8.

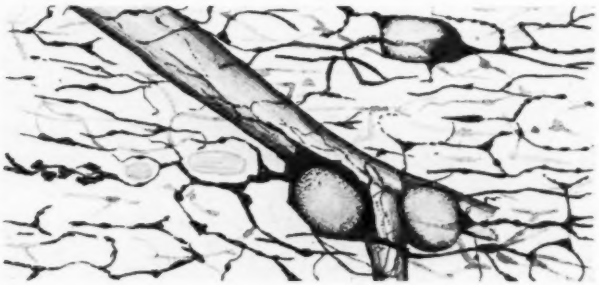

FIG. 7.—Oligodendroglia in cerebellar white matter, situated on vessel as a satellite.

Common neuroglia cells may be considered perineuronal or perivascular satellites in a different sense. It is not the cell body but the neuroglia expansions that are applied to the neuron and vessel. There is, however, the neuroglia cell with dense, moss-like expansions, described by Andriezen [6] and Cajal, whose cell body is plastered closely to vessels.

In addition to (i) the interfascicular glia or oligodendroglia of the white matter, and (ii) the perineuronal satellites, Rio-Hortega described a third type of oligodendroglia cell proper to the pons, bulb and spinal cord. These cells contain particularly large granules. They are plentiful in young animals at the time of maximum myelinization in these areas.

Small cells in groups of three to seven are to be found, especially

in the neuron centres of the bulb. These clusters are often situated next to nerve fibres. As seen in our preparations, the cytoplasm of these cells is scanty and their expansions few and poorly stained. The nature of these cells, and whether or not they represent a type of oligodendroglia peculiarly difficult to stain, does not seem altogether clear.

Origin and Relation to Neuroglia.

By recognizing that the satellites and interfascicular cells were of a different class from neuroglia and describing as a group the third element, Cajal [11] cleared up much vagueness of thought and presented the problem of further analysis of this element in concise form. In stating his belief that these cells were of mesodermal rather

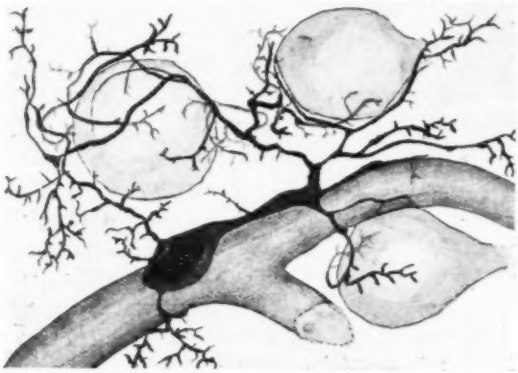

Fig. 8.—Microglia perivascular satellite from cerebral cortex.

than ectodermal origin he said that he did so "without prejudice against modifying our view if further discoveries alter the aspect of the question." After Rio-Hortega's description [18, 19] of microglia and oligodendroglia, composing the third element, Cajal confirmed the former entity and agreed to its mesodermal nature [12], but failed to stain oligodendroglia successfully. It is confusing therefore to cite (as Bailey and Hiller [7]) Cajal's reasons for the mesodermal nature of the "adendritic cells" as against Rio-Hortega's arguments for the ectodermal origin of oligodendroglia, as the first included cells (microglia) admitted by both to be mesodermal.

The same difficulty arises in considering the views of other writers with regard to the origin of the "indifferent cells." In the opinion of

Bevan Lewis, Robertson, Nissl, Bonome, Eisath, Schaper and others, these cells were undifferentiated or germinal neuroglia, and it seems probable that these investigators were studying for the most part oligodendroglia. On the other hand, Held, Alzheimer, Fieandt and others believed in a mesodermal origin; Rosental maintained that the function of these cells was to produce amœboid wandering cells, and investigators in the school of Alzheimer contended that they produced "Abbauzellen," cells active in areas of cerebral destruction. This last group of writers was, for the most part at least, studying microglia whose origin is mesodermal and which undergoes amœboid change to perform active service in areas of cell destruction.

Del Rio-Hortega has urged an ectodermal origin for oligodendroglia, believing it to be a specialized type of neuroglia, not germinal or undifferentiated neuroglia.

From a general structural point of view oligodendroglia resembles neuroglia strikingly. Both possess the asteroid body with expansions, centrosome and Golgi apparatus of similar appearance. The nuclei of the two forms differ only in size, and, most striking of all, oligodendroglia presents gliosomes similar in form, size, and general distribution to the gliosomes of neuroglia. Fig. 9 shows a series of oligodendroglia cells in the white matter whose prolongations are faintly stained, and a fibrous neuroglia cell (fig. 9, N). The gliosomes in both are intensely stained. Their form is round or oval. It will be noted that the granules in the neuroglia expansions are displaced to the surface protoplasm by the fibres in the centre of the expansion. On the other hand, the oligodendroglia expansion contains no fibres. Gliosomes therefore appear within the protoplasm of each expansion and not at the periphery.

The chief points of difference between the two types of cells may be illustrated by the same drawing (fig. 9): the difference of size and form of nucleus and expansion, the more direct and rigid shape of the fibrous prolongations, and the presence in them of fibres. But the structural feature which serves most completely to differentiate oligodendroglia from the classical neuroglia is the possession by the latter cells of sucker processes (vascular feet, fig. 9, V.F.). In spite of this, however, it is often difficult to decide with certainty whether a cell is a large oligodendroglia or a small neuroglia cell, for example M, fig. 2.

Similar staining reactions mean little, for, as was seen in fig. 9, it is possible to stain the two cell types simultaneously with silver carbonate. Gold chloride fails to stain oligodendroglia but stains both

protoplasmic and fibrous neuroglia. Many methods which preceded that of Cajal stained fibrous neuroglia and left protoplasmic neuroglia out of the picture, but it should not therefore be urged that the protoplasmic cells are not neuroglia. No more should the fact that Cajal's

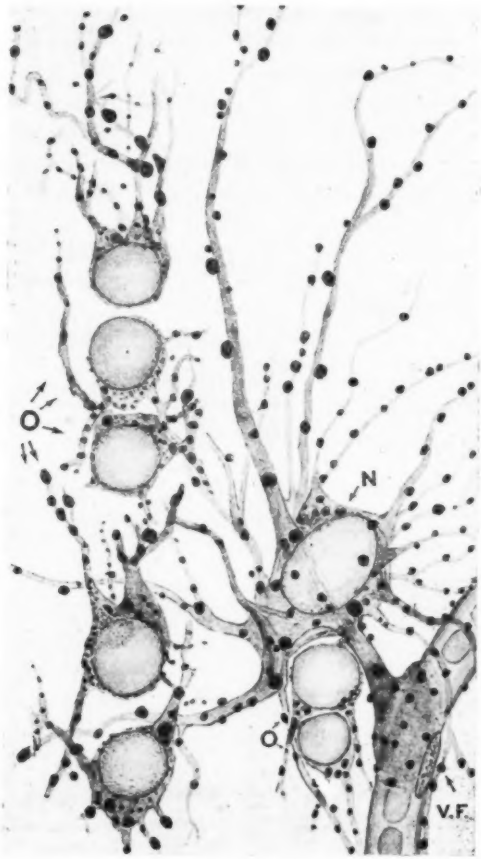

FIG. 9.—Cerebral white matter of rabbit stained by Del Rio-Hortega's method for gliosomes. The gliosomes in the oligodendroglia (O) are similar in form and stainability to those in the neuroglia protoplasm (N).

gold chloride method stains only the classical neuroglia be considered an argument against a common origin for these cells and oligodendroglia.

Apart from the structural similarity in fully developed forms of these cells, intermediate stages can be seen in young animals. Fig. 3 was drawn from the white matter of the cerebellum of a kitten of eight days. Interfascicular cells are present singly and in rows, and in general they show many of the characteristics of adult oligodendroglia (fig. 3, O). Fully developed neuroglia cells could be seen in areas not drawn. Cells T_1 and T_2 of fig. 3 are possessed of granular expansions exactly similar to those of the other young oligodendroglia cells, but they have also developed long expansions typical of neuroglia. The difference in size of the nuclei between fully developed neuroglia and oligodendroglia is not yet present. This transition explains the constant appearance of intercalated neuroglia cells in the rows of interfascicular oligodendroglia.

Certain spongioblasts therefore seem to develop into neuroglia and others into oligodendroglia. As has been said, Cajal showed that every neuroglia cell could be found to possess one or more vascular feet (suckers). Oligodendroglia expansions have no such terminations. It is, perhaps, justifiable to assume that, due to certain unknown influences, some cells acquire vascular attachments and immediately begin to take on the characteristics of neuroglia.

Achúcarro, in an interesting study [4] of the phylogenetic development of the neuroglia footplate, found that it was impossible to discover any cells corresponding to the "third element" in fishes. The ependymal glia cells in these forms do not possess vascular attachments. But in the lizard he found autonomous neuroglia with well developed vascular feet for the first time. Moreover a numerous group of cells appeared in this species which had the characteristics of the "third element of Cajal." These cells were found chiefly in the optic chiasma and commissures of the lizard. They probably correspond to interfascicular oligodendroglia.

Thus, it is reasonable to assume that both in the ontogenetic and philogenetic development, the appearance of the sucker process accompanies the differentiation of common or classical neuroglia from oligodendroglia.

Neuroglia possesses the ability to reproduce by amitotic division, a process which becomes very active under pathological conditions, each daughter cell possessing its own vascular attachments. In this process oligodendroglia seems to take no part. It should, therefore, not be looked upon as germinal neuroglia but as a type of cell which, in developing from its embryonic ependymal cell, has acquired a specialized

function. It might be looked upon as a subdivision of neuroglia along with the fibrous and protoplasmic forms, as Rio-Hortega proposes. But because of its evidently different function and its failure to react to pathological conditions as does neuroglia, it seems better to classify it as a distinct type of interstitial cell, bearing in mind that like neuroglia it develops from emigrant spongioblasts.

Conclusion.

In brief, the group of adventitial cells separated by Cajal from neuroglia under the name of "third element" has been shown by Del Rio-Hortega to be composed of oligodendroglia and microglia.

Mesoglia, which corresponds to oligodendroglia, was described by Robertson in 1900. But with all due respect to the memory of the Scotch scientist, it is best to drop the term mesoglia as the cells which he was the first to describe are apparently not of mesodermal origin.

Oligodendroglia cells appear in great numbers in the white matter where they form with their vine-like prolongations an incomplete investment for the myelin sheaths. In the grey matter these cells are chiefly disposed around neurones forming, with microglia, the perineuronal satellites.

Structurally, the resemblance of oligodendroglia to the classical neuroglia is striking, as it has similar gliosomes, centrioles, and Golgi apparatus, and nuclei which differ only in size and amount of chromatin. But the former cells are smaller, never develop fibres and have no vascular foot plates. It was shown that in mammals a few days old evident transition forms between oligodendroglia and neuroglia are to be seen (fig. 3), and it is suggested that this differentiation corresponds with the development, by certain emigrating spongioblasts, of vascular feet. The other spongioblasts do not form vascular attachments but develop characteristics of adult oligodendroglia. This explains the frequent presence within rows of oligodendroglia of intercalated fibrous neuroglia cells.

The work of Achúcarro was also cited above to show that in phylogenetic development the appearance of autonomous neuroglia with vascular foot plates corresponds with the first appearance of "third element" cells in the white matter, which are probably oligodendroglia.

Oligodendroglia might therefore be considered a type of neuroglia in so far as they have the same origin. But the two cell groups have developed different characteristics, apparently corresponding to distinct functions. And even under pathological conditions no change of cells

from one group to the other can be discovered, although transitions between protoplasmic and fibrous neuroglia under these conditions are numerous and hyperplasia of neuroglia takes place as the result of amitotic division, a process in which oligodendroglia seems to play no part.

Finally, the interstitial cells of the central nervous system may be roughly grouped under three general headings: (1) Classical neuroglia; (2) Oligodendroglia; (3) Microglia. For the sake of brevity, this may be expressed in a table.

Interstitial cells	In white matter	In grey matter
(1) Neuroglia, classical (ectodermal) ..	Fibrous	Protoplasmic
(2) Oligodendroglia (probably ectodermal)	Interfascicular ..	Perineuronal (satellite)
(3) Microglia (probably mesodermal) ..	Present (no subdivision)	Present and numerous (no subdivision)

Certain mental additions should be made to such a table, among which are the following: There are mixed (fibrous and protoplasmic) neuroglia cells. There are the special perivascular neuroglia cells of Andriezen. There are peculiarly large interfascicular oligodendroglia cells in the caudal part of the brain-stem. And microglia presents a number of different forms in new-born animals and under pathological conditions.

The function of oligodendroglia cells is not settled, but their relation to nerve cells and medullary sheaths corresponds strikingly with the relation of the subcapsular cells to the neurons of the spinal ganglia, and that of the sheath of Schwann cells to peripheral nerves. Moreover, oligodendroglia cells appear in the central nervous system at the time of maximum myelinization, and contain unusually large cytoplasmic granules which suggest a secretory function. These facts, as well as the arrangement of the cells along the medullary tubes, make it probable that they have to do with the elaboration and maintenance of myelin.

It is a pleasure to thank Dr. Ramon y Cajal and Dr. Del Rio-Hortega for the courteous hospitality extended to me in the laboratories of Madrid.

BIBLIOGRAPHY.

[1] Achúcarro, N. "Cellules allongées et stäbchenzellen, cellules névrogliques," *Trabajos del Lab. de Inv. Biol.*, 1909, **7**, 201-215.

[2] *Idem.* "Darstellung von neugebildeten Fasern des Gefässbindegewebes in der Hirnrinde durch eine neue Tannin-Silber Methode," *Zeitschr. f. d. g. Neurol. u. Psychiat.*, 1911, **7**, 4.

[3] *Idem.* "Contribution al estudio gliotectónic de la corteza cerebral," *Trabajos del Lab. de Inv. Biol.*, 1914, **12**, 229-272.

[4] *Idem.* "De l'évolution de la névroglie et spécialement de ses relations avec l'appareil vasculaire," *ibid.*, 1915, **13**, 169-212.

[5] ALZHEIMER, A. "Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe," *Histolog. u. histopatholog. Arb., Nissl-Alzheimer*, 1910, **3**, 401-554.

[6] ANDRIEZEN, W. "On a System of Fibre-Cells surrounding the Blood-vessels of the Brain of Man and Mammals and its Physiological Significance," *Internat. Monatsschr. f. Anat. u. Physiol.*, 1893, **10**, 533-540.

[7] BAILEY, P., and HILLER, G. "The Interstitial Tissues of the Central Nervous System: A Review," *Journ. Nerv. and Ment. Diseases*, 1924, **59**, 337-361.

[8] BIELSCHOWSKI, M. "Silberimprägnation der Neurofibrillen," *Neurolog. Centralbl.*, 1903, **22**, 1.

[9] CAJAL, S. RAMON. "Fórmula de fijación para la demonstración fácil del aparato reticular de Golgi, etc.," *Trabajos del Lab. de Inv. Biol.*, 1912, **10**, 221-246.

[10] *Idem.* "Sobre un nuevo proceder de impregnación de la neuroglia y sus resultados en los centros nerviosos del hombre y animales," *ibid.*, 1913, **11**, 219-237.

[11] *Idem.* "Contribución al conocimiento de la neuroglia del cerebro humano," *ibid.*, 1913, **11**, 255-315.

[12] *Idem.* "Algunas consideraciones sobre la mesoglia de Robertson y Rio-Hortega," *ibid.*, 1920, **18**, 109-127.

[13] *Idem.* "Una modificación del método de Bielschowsky para la impregnación de la neuroglia común y mesoglia y algunos consejos acerca de la tecnica del oro-sublimado," *ibid.*, 1920, **18**, 129-141.

[14] CERLETTI, U. "Studi recenti sull' istogenesi della nevroglia," *Annali dell' Istituto Psichiatrico della R. Univ. d. Roma*, 1908, **6**.

[15] COLLADO, C. "Participación de la microglía en el substratum patológico de la rabia," *Bol. de la Soc. Española de Biol.*, 1919, **9**, 175-190.

[16] DA FANO, C. "Osservazioni sulla fine struttura della nevroglia," *Labor. anat. norm. d. R. Univ. Roma e altri lab. biol.*, 1906, **12**, 1-75.

[17] DEL RIO-HORTEGA, P. "Noticia de un nuevo y fácil método para la coloración de la neuroglia y del tejido conjunctivo," *Trabajos del Lab. de Inv. Biol.*, 1918, **15**, 367-378.

[18] *Idem.* "El 'tercer elemento' de los centros nerviosos. I.—La microglia en estado normal. II.—Intervención de la microglia en los procesos patologicos. III.—Naturaleza probable de la microglia," *Bol. de la Soc. Española de Biol.*, 1919, **9**, 69-120.

[19] *Idem.* "La microglia y su transformación en células en bastoncito y cuerpos granulo-adiposos," *Archivos de Neurobiologia*, 1920; also *Trabajos del Lab. de Inv. Biol.*, 1920, **18**, 37-83.

[20] *Idem.* "Coloración rápida de tejidos normales y patológicos con carbonato de plata amoniacal," *Trabajos del Lab. de Inv. Biol.*, 1920, **18**, 31-108.

[21] *Idem.* "Estudios sobre la neuroglia.—La glia de escasas radiaciones (oligodendroglia)," *Boletin de la Real Sociedad Española de Historia Natural*, January, 1921.

[22] *Idem.* "El 'tercer elemento' de los centros nerviosos. Histogénesis y evolución normal; éxodo y distribúción regional de la microglia," *Memorias de la Real Sociedad Española de Historia Natural*, 1921, **10**, 213-268.

[23] *Idem.* "Una sencilla técnica para teñir rápidamente neurofibrillas y fibras nerviosas," *Bol. de la Real Sociedad Española de Historia Natural*, 1921, **21**, 364-371.

[24] *Idem.* "¿Son homologables la glia de escasas radiaciones y la célula de Schwann?" *Bol. de la Soc. Española de Biol.*, 1922, **10**.

[25] FIEANDT, H. "Eine neue Methode zur Darstellung der Gligewebes, etc.," *Arch. f. micros. Anat.*, 1910, **76**.

[26] GANZ, A. "Del Rio-Hortega's Derde Element in het centrale zenuwstelsel," *Nederland Tijdschrift voor Geneeskunde*, 1923, 67, **2**, 1024-1027.

[27] GOLGI, C. "Sulla fina anatomia della sistema nervoso," 1886. (See "Opera Omnia.")

[28] GORRIZ, M. "Quelques observations sur la composition des bains d'argent dans les méthodes de Bielschowsky et leurs variantes, et résultats du procédé de Bielschowsky-Cajal appliqué à l'histopathologie," *Travaux du Laboratoire de Rech. Biol. de l'Univers. de Madrid*, 1924, **22**, 169-190.

[29] HELD, H. "Über den Bau der Neuroglia und über die Wand der Lymphgefässe in Haut und Schleimhaut," *Abhandl. d. mathem.-physikal. Klasse d. kgl. Sächs. Gesellsch. d. Wissensch.*, 1903, **28**.

[30] *Idem.* "Über die Neuroglia marginalis der menschlichen Grosshirnrinde," *Monatschr. f. Psychiatr. u. Neurolog.*, 1909, **26**, 360-416.

[31] MARINESCO, G. "La cellule nerveuse," *Encyclopédie scientifique*, **2**, Doin, Paris.

[32] METZ, A. and SPATZ, H. "Die Hortegaschen Zellen (= das sogenannte 'dritte element') und über ihre functionelle Bedeutung," *Zeitschr. f. d. gesamte Neur. u. Psych.*, 1924, **89**, 138-170.

[33] NISSL, F. "Zur Histopathologie der paralytischen Rindenerkrankung," *Histologische u. histopathologische Arbeiten, Nissl-Alzheimer*, 1904, **1**, 315-494.

[34] PENFIELD, W. "Microglie et son rapport avec la dégénération névrogliale dans un gliome," *Trav. du lab. de recherches biol. de l'Univ. de Madrid*, 1924, **22**, 277-293.

[35] *Idem.* "Microglia and the Process of Phagocytosis in Gliomas," *American Journ. of Pathology*, 1925, **1**.

[36] ROBERTSON, W. "On a New Method of obtaining a Black Reaction in Certain Tissue-Elements of the Central Nervous System (Platinum Method)," *Scottish Med. and Surg. Journ.*, 1899.

[37] *Idem.* "A Microscopic Demonstration of the Normal and Pathological Histology of Mesoglia Cells," *Journ. of Ment. Science*, 1900, 724.

[38] *Idem.* "A Text-book of Pathology in Mental Diseases," 1900, Clay, Edinburgh.

[39] WEIGERT, C. "Beiträge zur Kenntnis der normalen menschlichen Neuroglia," Frankfurt, 1895.

ENCEPHALITIS PERIAXIALIS DIFFUSA.

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It is my purpose to draw attention to two cases which have within a short space of time come to autopsy. The results of macroscopical and microscopical examinations, though not identical, were of such great interest and corresponded so closely that it appears desirable to publish them, and at the same time to give a review of the literature of a comparatively rare and peculiar disease.

Case 1.—Mrs. A., born on April 19, 1889, a married woman and mother of five children, was admitted into the "Valeriuskliniek" at Amsterdam, on August 27, 1921. Her father was addicted to drink, one sister suffered from nervous attacks and her mother was nervous. No particulars were known concerning her youth except that she had been a good pupil at school. She had complained of a painful spot on the head for years, There had been no miscarriages; her last confinement occurred on June 28, 1921, that is, exactly two months before her admission to the hospital. After the childbirth, which was without any complications, the patient complained of dizziness: she sometimes had to catch hold of objects to prevent herself from falling and she occasionally overthrew things or dropped them. She had also a peculiar way of putting things beside the table instead of on it. She occasionally felt shocks, starting from her head, which affected her whole body. She could no longer estimate distances; she would go to the door and did not know when she had reached it. Though she often felt sick she did not actually vomit; lately she suffered from headache and everything seemed to whirl before her eyes. She complained frequently of heaviness and loss of power in her left arm. She was constantly worrying about herself and feared she would go mad.

The patient complained of being dizzy; objects she looked at did not appear to turn round, but she felt as if she herself were being moved up and down, as in a boat. On bending quickly this symptom became worse. Lately she had a buzzing noise in her right ear and she believed she had become deafer. She had frequent attacks of pain behind her right ear and a feeling of rigidity in her neck. Her eyesight had deteriorated and she found it more difficult to measure distances. At times she had visions of men and animals, or stars.

Somatic examination showed that the patient was anæmic and had slight albuminuria, but no casts were found in the sediment. Her blood-pressure was 120. Percussion of the skull caused no pain. There was a left-sided hemianopia; the left vision was $\frac{1}{2}$, the right 1. The optic discs on both sides were congested, particularly the left. The functions of her other cranial nerves were intact. There were no auditory disturbances. Sensibility of all qualities was unimpaired. Only an upper abdominal reflex could be obtained; it was slight but equal on the two sides.

September 3. While lying in bed quietly she felt as if she moved, and she complained of a disagreeable feeling when sitting up and of headache and dizziness.

September 5. More headache than before; also pain in the neck.

September 9. Patient had an epileptic fit; she made a noise, turned head and eyes to the right, moved both arms, but especially the right, drew up her legs and ground her teeth. For a few minutes she was comatose, with a pulse-rate of 36. She lay on her left side, and saliva dribbled from her mouth. A very doubtful Babinski reflex was present on the left side. No incontinence occurred. After this fit she was disoriented, drowsy and amnesic for some hours. Her pulse became gradually normal. She remembered nothing of the attack.

September 12. The Wassermann reaction in her serum was 0·2. The Wassermann reaction in her cerebrospinal fluid was negative, but this was under high pressure. The Nonne reaction was slightly positive but there was no pleocytosis.

September 17. Increasing headache, drowsiness, and a slow irregular pulse (40-60) varying in frequency and in volume. The cerebrospinal fluid was at a pressure of 65 cm. After lumbar puncture the pulse was quicker, though still irregular. Nonne's reaction was still slightly positive, but the Wassermann test was negative and there was no pleocytosis.

After the puncture there was, for a short time, improvement in her general condition, but owing to her poor pulse, the epileptic fit and an increasing drowsiness, trepanation was decided upon. The congestion of the optic discs and high fluid pressure gave rise to the suspicion of a tumour or cyst. The hemianopia, subjective visual perceptions in the blind parts of the visual fields and a suspicion of an "uberschüssiges Gesichtsfeld" pointed to disease of the occipital lobe.

September 20. Operation. Neither trepanation nor puncture revealed anything abnormal at the right occipital pole.

September 27. Patient felt better but complained of double vision. The fundi remained unchanged.

October 5. Eyesight and hearing diminished rapidly. Patient vomited once or twice.

October 12. General condition rather good, but the patient complained of headache.

October 24. General health satisfactory, but the patient was psychically

on the decline. She no longer recognized her physician and was scarcely able to perform any order. There was perseveration of orders once given and successfully executed. Vision was so much reduced that she could no longer fix individuals in her room, and she spoke to persons who were not present. After severe attacks of frontal headache she had violent fits of screaming.

October 28. Patient returned home. Left and right vision $\frac{1}{10}$ at the most. There were no longer any disturbances in the fundi. More accurate examination was impossible.

On February 8, 1923, the patient was examined at home; naturally this examination could be only incomplete. The most striking symptoms were: paresis of both legs and of the right arm, and tenderness of the right leg. The right Achilles reflex brisker than the left. She had now developed cystitis and severe bed sores, was very drowsy and could not recognize any one.

On February 28, the patient died. The brain was removed five hours after death.

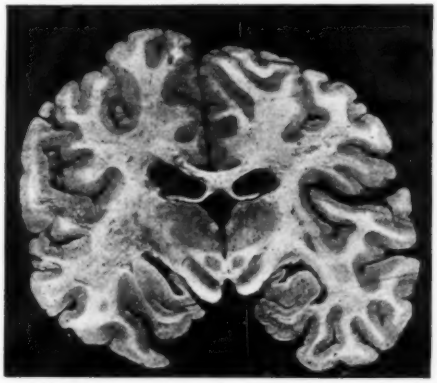

FIG. 1.

After being hardened in formol the brain was divided into frontal sections. The white matter of both hemispheres was of a peculiar greyish-yellow colour, especially in the occipital lobes (fig. 1), but also in the parietal and temporal lobes. The posterior horn of the right ventricle showed a large cystic distention towards the occipital pole; in consequence of this, the posterior part of the occipital pole was formed only by a membrane about 2 mm. in thickness, the inner wall of which was continuous without any sharp demarcation with the ventricular lining. Even if the operation did not produce the cyst, this must have enlarged considerably after the operation; otherwise it is difficult to account for the fact that punctures during the operation did not yield any fluid, unless brain matter had blocked the puncture needle.

Histological examination by the methods of Weigert-Pal, Bielschowsky,

hæmatoxylin-eosin, Mann-Alzheimer, Achucarro, Nissl, and fat- and glia-stains, disclosed the following changes:—

Myelin sheaths.—The greater part of the myelin sheaths in the white matter had disappeared; high magnification showed only the presence of a few

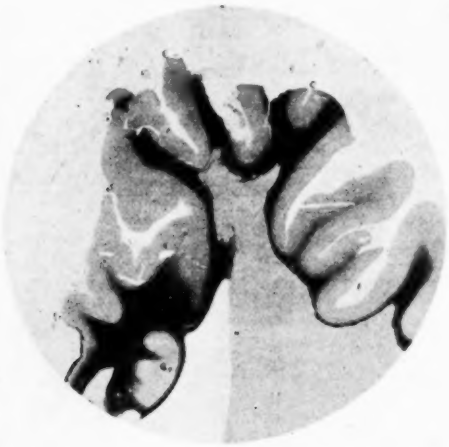

FIG. 2.

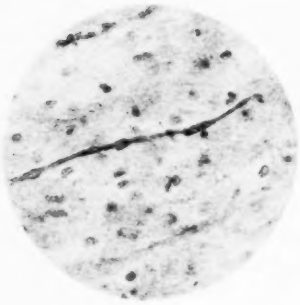

FIG. 3.

scattered sheaths with marked varicose distentions (fig. 3). The subcortical fibre layer persisted but it was nibbled into from within in places (fig. 2). Accumulations of fat of extraordinary size were present in the areas in which the myelin sheaths were degenerated.

Vessels.—The number of the vessels had increased and their adventitial coats contained dense infiltrations of cells of the following types (fig. 4): (1) the majority were lymphocytes, a great number of which had a clearly marked protoplasmic zone; (2) elements resembling degenerated plasma cells which stained metachromatically and had uncoloured spaces in the neighbourhood of the nuclei and at some distance from them; they were rather angular in outline and contained vacuoles; (3) single "mast cells"; (4) scavenger cells which were generally rare, but in places they formed the greater part of the perivascular infiltration; (5) oval nuclei similar to swollen endothelial nuclei, containing green pigment; (6) extremely large, swollen, pale nuclei, resembling the nuclei of "gemästete" glia cells. Many of the endothelial cells of the infiltrated vessels had swollen nuclei. The cortex and pia were free from infiltration.

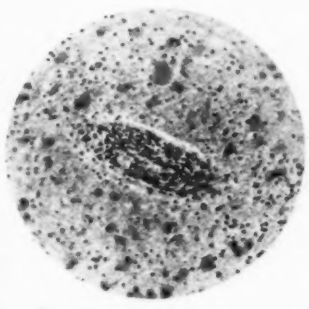

FIG. 4.

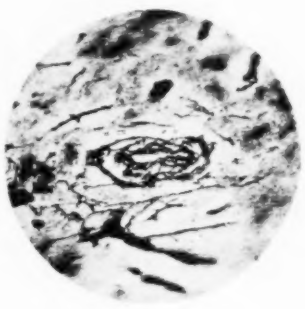

FIG. 5.

Achucarro's stain showed a pronounced increase of the mesenchymatous tissues, which had invaded the brain tissue and formed nets between the vessels (fig. 5).

Axons.—All the axis-cylinders probably persisted, but by far the large part of them stained very feebly by Bielschowsky's method; a few, certainly more in number than the retained myelin sheaths, were fairly well impregnated, but were of irregular calibre and presented occasional varicose distentions (fig. 6). Outside the affected area they were perfectly normal, even when separated from the cortex by a patch of disease.

Glia.—There were numerous changes in the neuroglia: (1) Scavenger cells (see Vessels) were diffusely scattered throughout the tissue, and in addition structures resembling developing scavenger cells; slight changes could be observed in the shape of the naked glial nuclei, which were occasionally surrounded by metachromatic protoplasm. (2) "Gemästete" glial

cells (fig. 7) with moderately large nuclei which were frequently of irregular outline and occasionally two or more in one cell, and a very large cell body of plain outline, smooth or finely granular and highly coloured by eosin; these were scattered throughout the tissue and were, as a rule, greater in number near the vessels. (3) Many glial nuclei of irregular outline, some-

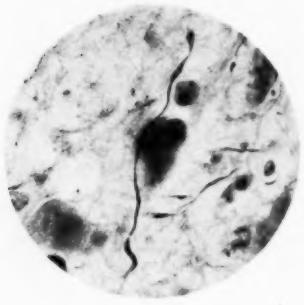

FIG. 6.

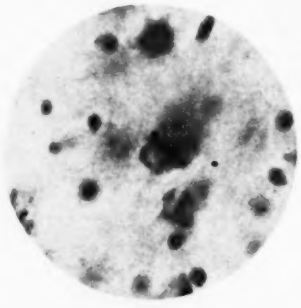

FIG. 7.

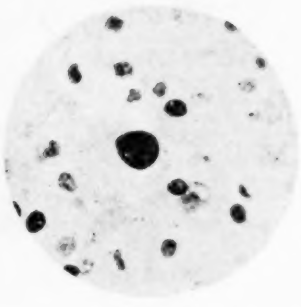

FIG. 8.

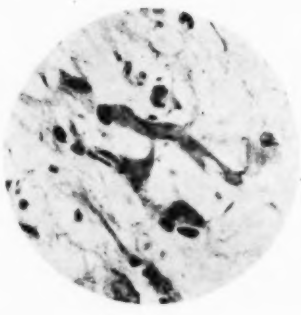

FIG. 9.

times arranged radially in clumps. (4) Dense structures (fig. 8) the size of several nuclei, which stained by every nuclear stain and sometimes gave the impression of karyorrhexis (monster glial nuclei). (5) Monster glial cells of pollarded-willow shape (fig. 9). (6) A great development of glial fibres (fig. 10). Fat droplets were found in abundance when fat stains were employed.

The *brain-stem* presented no evidence of secondary degeneration, but

numerous small, sharply outlined demyelinated spots were found. These were exactly similar to those found in early patches of multiple sclerosis (fig. 11).

From a clinical point of view the case offered peculiar difficulties. Certain symptoms led to the diagnosis of a tumour or cyst, and trepanation was therefore performed. The grave general symptoms pointed to a severe brain disease, but a definite diagnosis could not be made.

Pathological examination showed that by far the greater part of the hemispheres had undergone a greyish-yellow change which was, how-

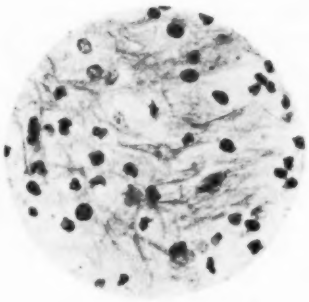

FIG. 10.

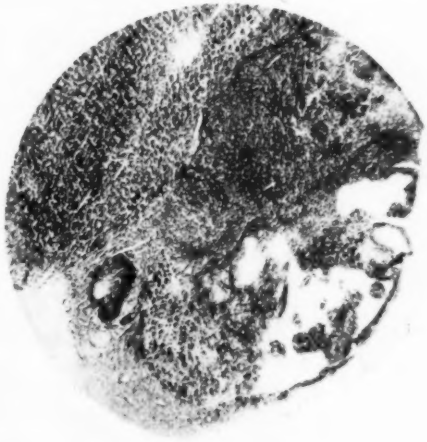

FIG. 11.

ever, limited to the white medullary matter. Histological examination revealed disappearance of the myelin sheaths with but few exceptions, and considerable changes in those which remained. The fibræ arcuatæ, however, were unaffected.

The next striking feature was the dense infiltration of the adventitial coats of the vessels with lymphocytes, a smaller number of cells similar to plasma cells, "mast" cells, scavenger cells, oval nuclei, swollen endothelium-like nuclei and pale swollen nuclei similar to the nuclei of "gemästete" glia cells. Many of the endothelial cells of the infiltrated vessels contained swollen nuclei. An increase of mensenchymatous tissue was observed forming nets between the vessels.

The axons persisted, but staining revealed a considerable change in the majority of them. This explains the absence of secondary degeneration of the brain-stem; unfortunately it was not possible to obtain the spinal cord for examination.

Hæmatoxylin-eosin preparations revealed "gemästete" glia cells containing one or more nuclei, which were most numerous close to the vessels. Further, many glial nuclei of irregular shape, fibre clews, monster glia cells and an excessive development of glia fibres were present. Scavenger cells were found in relatively small numbers both around the vessels and freely scattered through the tissue.

Finally, changes were observed in the brain-stem exactly similar to those which occur in patches of multiple sclerosis.

Case 2.—A young unmarried man of 20 was admitted into the asylum of Wolfhezen (January 15, 1919) with the following history: He was delivered by application of the forceps, had been very backward from birth; was long in becoming clean and learned to walk rather late. Until he reached the third form all went well at school, but he made no further advance. He read slowly and was scarcely able to write or cipher. He was clumsy and was inclined to make stereotyped movements with his body; he masturbated frequently. In his youth he suffered from rickets. His sister was backward too. The diagnosis of imbecility was made. When intelligence tests were applied many defects were discovered.

In June, 1920, an ataxic gait and a tendency to fall were noted.

August 4, 1921. Patient had epileptiform attacks in which both the head and eyes turned towards the right. In addition to these fits he was subject to convulsions which involved the right half of the face and the right arm and leg, and at times spread over the whole body. During the fit the left arm was flexed in a tonic attitude near to the head; no convulsions were observed in the left arm. The left leg was also in tonic contraction, but sometimes convulsed too.

Two hours after the attacks ceased the right arm was very weak, the left spastic and the right corner of the mouth drooped; the right leg was weak and the left spastic. The abdominal and arm reflexes could be obtained. The knee-jerks were very brisk, the left rather more than the right, and the Achilles-jerks were also brisk. Babinski's sign was not present.

August 13. Upward and downward movements of right hand and arm occurred; the right leg was continually flexed at the knee and hip, and the head was rigidly turned towards the right. The left arm was weak and the right spastic; slight clonic movements of the right foot and calf muscles occurred, the foot being in the varus position. Babinski's sign was present on the right side. The left foot was weak and spastic, but Babinski's sign was not obtained. The knee-jerks were brisk but the Achilles-jerks were normal. The right leg was hyperalgesic. When the left leg was pricked the right was

drawn up and the left moved slightly; pricks on the left foot caused dorsal flexion of all toes. Otherwise sensibility to touch and pain were not disturbed.

Pricking the paralysed left arm caused abnormal movements of the right arm. The pupils were dilated and the eyes turned towards the right.

August 19, September 2, September 9, September 18. Seizures which ceased on the administration of amylene hydrate.

October. Patient scarcely spoke and there seemed to be some disturbances of speech. He frequently moved his upper and lower limbs; the right leg was constantly kept rigidly flexed at the knee and hip.

November. A condition of progressive dementia. Patient laughed or cried on being addressed, but answered no questions and hardly spoke, but he often whined and moaned.

January 2, 1922. Patient became comatose; after about half an hour he began to vomit and developed convulsions of the whole body. Epileptiform fits occurred at irregular intervals which could not be controlled by amylene hydrate. Temperature rose to 40° C.

January 3. The left arm was in constant motion and the left corner of his mouth twitched. The left leg, which was not now paretic, was sometimes drawn up, but more commonly extended. There was no paresis of the right arm, but the right leg was very spastic and dropped inertly when lifted up. The abdominal reflexes could not be evoked, but the tendon reflexes of the lower limbs were normal. Babinski's sign was obtained on the left side but not on the right. The head and eyes were turned towards the left, and there were slight convulsions of the left arm. The patient was very drowsy and moaned continually.

January 5. The patient had fifty-two fits.

January 6. Only two slight seizures; comatose.

January 7. Stationary coma: when the lips were touched the patient opened his mouth widely.

January 9. Died.

The brain was sent to me for investigation. Naked-eye examination detected the same spotty changes as were visible in the preceding case. These changes were present on both sides throughout almost the whole hemispheres, but were more pronounced and more gelatinous than in the first case. In the left hemisphere there was some internal hydrocephalus.

Histological examination was carried out by the same methods as those employed in the first case.

Myelin sheaths.—A considerably larger number of myelin sheaths was preserved than in Case 1. The fibræ arcuatæ were unaffected and no secondary degeneration was found.

Vessels.—There was no increase of vessels in the affected areas, and those present were not infiltrated except close to the periphery of the lesion. Here there was a distended meshwork of perivascular lymph spaces with some connective tissue nuclei and some scattered lymphocytes, indicating different stages of the disease.

Axons.—Many axons appeared pale, but a much greater number than in Case 1 stained well. Some of them only were slightly swollen.

Glia.—In the demyelinated area the intermediate substance consisted of many glial fibres which were prolongations of elements similar to "gemästete" glia cells (fig. 12). These glia cells had large nuclei, sometimes two, but they were smaller than in Case 1. All remaining glial nuclei had compact protoplasmic zones around them. Green pigmented scavenger cells were also present (see Cortex), but there was very little fat apart from scattered droplets in the vessel walls.

The *pia* was swollen in this case. In some small areas the connective tissue was not visible, being replaced by pale swollen nuclei and bands of metachromatic protoplasm. Similar cells also appeared in those areas where connective tissue was found: in these places many of them passed over into

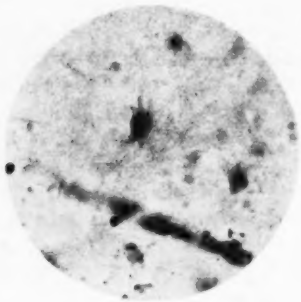

FIG. 12.

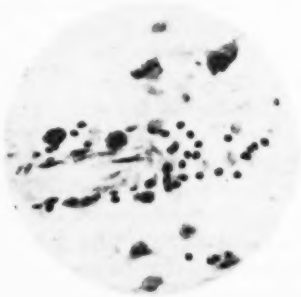

FIG. 13.

connective tissue cells. In the external layers of the pia there was a diffuse infiltration of round cells with many "mast" cells among them.

Cortex.—In the lamina zonalis there was no perivascular infiltration, but it presented evidences of glial activity. In the fifth cortical layer there was some perivascular infiltration (fig. 13), more particularly around the larger vessels, by lymphocytes which possessed a varying amount of protoplasm and indented nuclei. These same cells also appeared as satellites. Large scavenger cells could be seen between the lymphocytes (fig. 14), some of which were packed with green pigment. Many ganglion cells of the fifth and sixth cortical layers had undergone tigrolysis and were surrounded by satellites. Little evidence of glial activity could be seen, but some rod cells were probably present.

Numerous clumps of pigment existed in the deepest layer of the cortex (fig. 15); it was brownish-green in colour and consisted of fine granules or droplets. In or upon them small elongated nuclei could be sometimes

observed. Similar clusters of pigment occurred in the subcortical layer and in the fibræ arcuatæ. Here nuclei were more numerous.

The ganglion cells, especially those of the frontal region, contained many fat droplets.

Striatum.—No disease was discovered in the corpus striatum. In the pallidum there were many clusters of pigment.

The *cerebellum* exhibited congenital anomalies, in the form of asymmetrical aplasia, with secondary atrophy of the pons.

A positive clinical diagnosis could not be made in this case either. Here, too, the symptoms suggested a generalized diffuse disease of the brain, the exact nature and localization of which could not be determined. Epileptiform attacks constituted the outstanding feature of

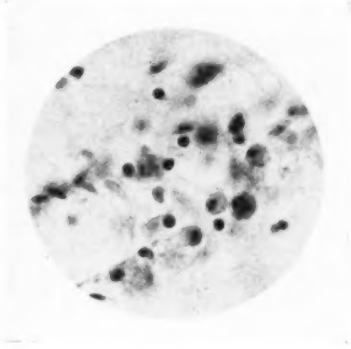

FIG. 14.

FIG. 15.

the disease but gave no help in the diagnosis, for at first right-sided convulsions were observed, followed by a flaccid paresis; while a fortnight later there was a left-sided paresis with a flaccid arm and a spastic lower limb, and on the right side, more particularly in the leg, abnormal movements and spasms. Five months afterwards the symptoms were reversed, there being left-sided convulsions with spastic paresis of the right leg.

Pathological examination showed even to the naked eye a surprising similarity to the changes found in Case 1. Here, too, the changes occupied almost the entire white matter of both hemispheres, and they appeared to be more severe, for the affected tissue was more gelatinous.

Compared with Case 1 a considerably larger number of myelin sheaths were preserved, and the fibræ arcuatæ were intact too. The

number of vessels was not increased and they were not infiltrated, with the exception of some of the vessels on the margin of the diseased area, round which there were connective tissue nuclei and lymphocytes. This points to a difference between the centre and periphery of the areas of disease.

The axons were also more normal than in Case 1, and no secondary degeneration was discovered; the spinal cord, however, was not available for examination.

The "gemästete" glial cells which occurred here were smaller than in Case 1. Many glial fibres, glial nuclei and green pigmented scavenger cells were seen. This case exhibited changes in the pia and the cortex was affected. In the outer layers of the pia a diffuse infiltration of round cells, interspersed with "mast" cells, could be

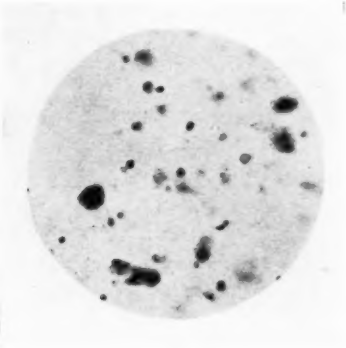

FIG. 16.

seen, and there was some perivascular infiltration by lymphocytes and large scavenger cells in the fifth cortical layer. Many ganglion cells of the fifth and sixth layers exhibited tigrolysis and were surrounded by satellites. There were many clusters of pigment in the sixth layer and between the fibræ arcuatæ; these were also present in the pallidum and ansa lenticularis. In my opinion these clusters were associated with scavenger cells, since it was possible to trace the gradual transition of green pigmented scavenger cells into these clusters (fig. 16).

The cerebellum exhibited congenital anomalies.

These two cases which had clinically so little in common showed pathologically a certain degree of similarity; both are characterized by

destruction of the white matter of both hemispheres, the fibræ arcuatæ, or more correctly the subcortical fibres, remaining unaffected.

These typical changes have already attracted attention, though not to the degree that might have been expected. When large brain sections are stained by the Weigert-Pal method or by carmine, such changes must be conspicuous, and yet Pierre Marie in 1914 [15] spoke of such a disease as a rare occurrence of which no case was recorded in the literature. In the description of a case called by him "sclérose intra-cérébrale centrolobaire et symétrique," which may pathologically be compared to our second case, Marie's statement was not quite correct, for even at that time a few cases had been described and submitted to careful histological examination. Of recent years, however, after my first case had already been published in extract and the study of the second begun, the number of recorded cases has largely increased, but almost exclusively in German literature. The lead was given by an article by Schilder [20] entitled: "Zur Kenntnis der sogenannten diffusen Sclerose." Heubner [9], it is true, had described in 1897 a disease under the name of diffuse brain sclerosis, in which post-mortem examination showed a diffuse sclerosis of the brain and spinal cord, the entire white matter of both hemispheres being unusually firm and resistent, but the absence of histological examination makes it difficult to determine whether this case belonged to the same group as those recorded here. In a case which corresponded clinically to Heubner's, Schmaus [22] speaks of an "inflammatory process," but neither in this case nor in Strümpell's [27] were myelin sheath stains employed. Further, Schmaus described an enormous atrophy of the brain which he assumed to be the sequel of an interstitial process, of which there was no evidence in my cases. Those cases in which myelin sheath stains were employed and no changes similar to those in my cases were found, must belong to another group. Thus Weiss [29] described a case of diffuse sclerosis of the brain and cord with symptoms which he styled "rigor spasticus universalis," in which microscopical examination showed relatively few histological changes.

On account of the great uncertainty about the cases recorded in the older literature, Schilder rightly gave the special name "encephalitis periaxialis diffusa" to the group defined by him. The remaining cases, of which our knowledge is less exact, may be grouped together under the name of diffuse sclerosis. It may be recalled that Marburg has suggested for multiple sclerosis the name "encephalomyelitis peri-axialis scleroticans." Both Spielmeyer [25] and Neubürger [16] have

suggested the name "sclerosierende Encephalitis des Haemisphaerenmarkes," since they regarded the lesions as non-inflammatory. Schilder's name implies a diffuse process in contrast to the circumscribed lesions of multiple sclerosis, and at the same time indicates the preservation of the axons. This criterion is not absolute any more than it is in multiple sclerosis, since in some cases nearly all the axons disappear. For this reason perhaps an indefinite title, as "sclerosing encephalitis of the white matter of the hemispheres" would be more correct. The same difficulty occurs as in encephalitis, since there are cases, to which I will revert presently, in which one can speak of a purely degenerative process more correctly than of an encephalitis. Further, cases in which there is but little infiltration of the vessel walls, instances of which will be mentioned presently, may be looked upon as intermediate and transitional types. The chief point is that the true inflammatory type, which is distinguished by the presence of the cardinal features of inflammation demanded by Lubarsch, that is: structural alteration (disappearance of myelin sheaths and change or partial disappearance of axons), proliferation (glial reaction) and exudation (vessel infiltration), as well as the degenerative and transitional forms, may be included in the one group. Their ætiology is probably the same too. It seems likely that a noxious element invades the central nervous system, or rather the brain only, by way of the blood-vessels; that the vessels play a part in its pathogenesis is proved by the fibræ arcuatæ remaining intact, for the fibræ arcuatæ and the cortex are supplied by the same blood-vessels, whereas the long vessels of the white matter come from the base of the brain (Obersteiner, Anleitung beim Studium der nervösen Zentralorgane). Since the white matter is exclusively affected one could speak of leucencephalitis, as Claude and Lhermitte [5] do of a case which, in my opinion, does not belong, though related, to the cases described here.

We can now pass on to a discussion of the histo-pathological features of the disease, and compare the changes I have found with the earlier observations recorded in literature.

There are two conditions which exhibit some kinship with the pathological process that interests us here, namely, diffuse glioma and multiple sclerosis. Confusion with the typical histological changes of pseudosclerosis, tuberous sclerosis, or the so-called "Merzbacher-Pelizaeus disease" is hardly possible.

Considerable difficulty may arise in the distinction from diffuse glioma, for cases of this condition are known in which, as in the cases

recorded here, the normal exterior configuration of the brain was preserved, the cortex was unaffected and the axons had suffered little or not at all. More commonly, however, the disease is not sharply demarcated from the normal brain tissue, and its histological structure is altered. The occurrence of choked discs and high pressure in the cerebrospinal fluid, associated with such symptoms as were present in my first case, might, however, lead to the conclusion that there was an increase of volume in the parts affected, producing raised intracranial pressure. But pathological examination proved that in my case we had to deal with a considerable decrease of volume, shown by the great distention of the posterior horn of the ventricle. The rise of intracranial pressure may have been a result of a primary inflammatory reaction. In several places the perivascular infiltration predominated over glial proliferations, while, as Neubürger has pointed out, distinct blastomatosis, changes in the cells, nuclei showing karyorrhexis, at the most a few scavenger cells around the vessels, and perhaps slight secondary inflammatory infiltrations, may be found at the periphery of a glioma. Walter mentions as a further characteristic of gliomata, that they tend to break through rather than reinforce the demarcation membranes of the vessels, a process of which there was no evidence in my cases. Cavity formation and softenings are also characteristic features of gliomata, but in Rossolimo's case [19] there was a cavity the lining of which differed in appearance from the wall of a ventricle, and there was no communication with the lateral ventricle. Rossolimo, however, regarded his case as a transition between disseminated sclerosis and gliosis, as it presented peculiarities of both these conditions.

It may be therefore difficult to differentiate this condition from gliomata, the more so since in some cases, as in those described by Cassirer and Lewy [3], gliomata contained scar tissue in the centre, a large number of the axons were well preserved, the periphery consisted of a very cellular tissue suggesting a status spongiosus, and the cortex was largely, though not absolutely, unaffected. Here there was a combination of very soft cellular and very firm fibrillar tumour tissue. According to Cassirer and Lewy, however, a characteristic of blastomatosis glial proliferation is that the cortex is affected to a certain extent and large masses which take up iron but contain no lime are found in the immediate vicinity of the disease. Even if there were no breach in the pia, as in the case described by Cassirer and Lewy, and the disease were entirely restricted to the white matter, it should be possible in most cases to diagnose the tumour by its structure, by the presence of

karyorrhexis, and by the arrangement and the mode of extension of its processes. But there can be no doubt that the morphological similarity between the periphery of inflammatory lesions and blastomatosis in the brain may be very great.

There is undoubtedly a close resemblance to multiple sclerosis, especially when, as in my first case, foci similar to those of multiple sclerosis were found in the brain-stem. These were also present in the cases described by Jakob [10], Stauffenberg [26], Rossolimo and perhaps also in that recorded by Beneke [1], who spoke of multiple patches. Patches of disease occupying almost all of both hemispheres and rigidly restricted to the white matter are exceptional. Further, the infiltrative changes and the proliferation of connective tissue fibrils are similar to those seen in multiple sclerosis, and in both diseases most of the axons are well preserved. In my cases and in others where the disease was indistinctly demarcated and tended to extend, the destruction of the axons coincided with that of the myelin sheaths. Marburg [14] positively states that the lesions in multiple sclerosis are fundamentally discontinuous, while they can certainly be regarded as continuous in my cases.

Siemerling and Creutzfeldt [24] attach importance to the fact that the larger patches, as in my cases, cannot be related to the area of one vessel; this is also a point of distinction from multiple sclerosis. They also point out that the patches of disease are not due to confluence of separate foci, since their shape and their internal structure, and the fact that the subcortical fibres of the convexities of gyri remain intact, are against this hypothesis. The lateralward extension of the disease might be determined by secondary degeneration of the adjacent parts of the white matter, but the inflammatory changes in these regions are against this view. Finally, there is the possibility that the extension of the noxious agent which produces the changes in the glial tissue might also determine the extension of the demyelinization so that the disease progresses towards the convexity and is arrested only when it has reached the fibræ arcuatæ, since these fibres are different in direction and histological structure, and are supplied by the same blood-vessels as the cortex.

When the pathological changes described in the literature are analysed it is found that though there are considerable differences the same essential features are found in all the cases recorded. These are: (1) preservation of the shape of the brain; (2) a large area of disease restricted to the white matter of the hemispheres and sharply

demarcated; (3) disappearance of the myelin sheaths with total or partial preservation of the axons; (4) the changes in the glia to which I have referred; (5) the infiltration of the sheaths of the vessels, but even in this there are exceptions.

When Schilder described his first case, he found in the literature only four instances which had been at all accurately examined, viz., those recorded by Rossolimo [19], Ceni [4], Beneke [1] and Haberfeld and Spieler [6]. Ceni looked upon his own case as one of glioma, and Beneke's description leaves much to be desired; Neubürger [16] regarded the latter case as a glioma too. Rossolimo looked upon his case as a transition between disseminated sclerosis and glioma, but it shows very great likeness to Schilder's. The brain of Haberfeld and Spieler's case has been submitted to a re-examination by Schilder, who included it among his cases of encephalitis periaxialis diffusa. I will henceforth refer to this as Schilder's second case. In Schilder's second publication he also mentioned a case described by Redlich [17], of which only a short report is existent, in which a large area of disease was found in the white matter of the right parietal and occipital lobes, but the cortex had remained intact. Though Redlich spoke of a gliomatose area with large glial cells and an abundant formation of glial fibres, he also found in many places lymphocytic infiltrations around the vessels and in the tissue, and occasionally also outside the large lesion. Hence it seems probable that this case belongs to the same group. This was the first case in which the disease was described in an adult, a woman of 41; in all the previous instances recorded children and youthful persons had been affected.

Of recent years several other cases have been recorded which either belong or are related to this disease; some of these cannot be yet unconditionally classified. In a case which Walter [28] describes but does not venture to classify, Weigert's stain was employed only several years after death, but it was obviously related to my second case. The white medullary sheaths were affected, but everywhere some thin sheaths remained; and the reduction of axons was on the whole parallel to that of the myelin sheaths, but they were generally more wasted than the sheaths. Sections showed large scavenger cells, often in clusters, in the neighbourhood of the vessels, as well as typical astrocytes. Degenerative forms, as those in Schilder's case, were not found anywhere, and there was a large increase of glial fibres, and plasmatic glia (Cajal) was met with in the transitional zone between the white matter and the cortex and in the deeper cell layer of the latter too. Vessels with

numerous round cells were not rare in the white matter. Almost the whole white matter of the hemispheres was involved by sclerotic changes. This case, and that described by Marie and Foix, were of much longer duration than the other cases described.

One of Henneberg's [7] two cases also leaves room for doubt (Henneberg, i). This author described foci of softening and assumed that the lesions of the brain were caused by inflammatory softenings probably as a result of stasis. In the distal part of the pons and in the medulla oblongata there was also a patch of infiltrative encephalitis which closely resembled that found in malignant multiple sclerosis. In the spinal cord there were diffuse degenerative and inflammatory changes; the degeneration of the white columns was somewhat similar to that found in funicular myelitis. In the ventral horns many ganglion cells showed the chronic alteration of Nissl. The pia mater was irregularly infiltrated by small round cells. The axons had disappeared from the affected areas, the glial cells had proliferated and a few of the larger vessels were infiltrated by small round cells. No particulars are reported on the state of the myelin sheaths. Neubürger included this case in the group described here, but owing to the comparatively short description of it some doubt on its real nature remains.

In the case described by Claude and Lhermitte [5], the lesions were most pronounced in the centrum ovale; on the one side they extended towards the cortex but left the convolutions unaffected, and on the other side particularly towards the nucleus lentiformis and the optic thalamus. The pathological changes spread up to the ependyma, underneath which there was an intense proliferation of the neuroglia, and as far as the radiations of the corpus callosum. The chief changes were: (1) inflammatory infiltration of the perivascular spaces and the walls of the blood-vessels by lymphocytes, with astrocytes, "monster" cells, and a multiplication of satellite cells; (2) necrosis leading to destruction of small portions of the brain, accompanied by macrophagia. Some vessels showed incipient thrombosis which may have caused the small necrotic foci. The nerve elements had completely disappeared, but the intensity of the glial proliferation and the character of the glia distinguished the softening in this case from that found in old people. There were amœboid cells, phagocytes engaged in the removal of the detritus, an increased number of astrocytes, and cells with enormous protoplasmic prolongations, indicating the existence of a toxic-infectious process in association with the necrobiotic lesions. This peculiar glial reaction was also found outside the areas of softening, in the zones only affected

by inflammation. There was, within the inflammatory foci, a considerable hyperplasia of the glial reticulum which contained fibrillar and protoplasmatic monster glial elements. The meninges were unaffected. The lesions were attributed by the authors to a toxic-infectious process producing inflammatory and necrotic changes of the central portions of both hemispheres, which probably spread from the one hemisphere to the other. There is considerable doubt from both the pathological and clinical sides as to whether this case should be classified with those described here.

Finally, Rochon-Duvignaud [18] have described a case in which they were surprised by the sudden onset of blindness as there was only very moderate and recent choked discs. Autopsy revealed bilateral lesions of the optic radiations to which the rapid loss of sight must be attributed rather than to the congestion of the optic discs. This did not, however, explain all the ocular symptoms. They compared this case with Claude and Lhermitte's. Horizontal sections of the brain revealed in the centrum ovale of the left hemisphere a liquified white matter resembling an abscess. This disease occupied the posterior half of the centrum ovale and extended round the lateral ventricle to the corpus callosum. Further in front there was a second smaller patch of encephalomalacia in the superior frontal lobe. In a lower section, at the level of the internal capsule, the disease occupied mainly the neighbourhood of the occipital horn of the lateral ventricle and sagittal layer of the left temporo-occipital thalamic radiation. It extended into the white matter of the gyrus subparietalis and of the gyrus fornicatus, and to the cortex of the lobus lingualis. In the white matter of the three convolutions of the frontal lobe there were necrotic foci which extended to the cortex in the third orbital gyrus. In the upper part of the left hemisphere there was a series of patches in the centrum ovale, some of which also affected the cortex, especially in the frontal region. A horizontal section of the upper part of the hemisphere revealed patches of encephalitis, almost exclusively in the white matter, particularly under the post-central gyrus, and a small isolated area in the white matter below the first frontal convolution.

Histological examination discovered in the occipital region of the right hemisphere a considerable decrease of myelin sheaths, particularly in the temporo-occipital projection-fibres of the thalamic radiations. Axon stains were not employed, at least no information on the changes shown by them is supplied. The vessels appeared to be little affected, but were infiltrated by lymphocytes. In the occipital region there

were newly-formed vessels with sclerotic walls and a more discrete infiltration by lymphocytes. In the central part of the affected area, especially in the neighbourhood of vessels, an intense proliferation of glia was seen, consisting of a fine reticulum filled with large astrocytes.

It is also doubtful if this case belongs to the group in which we are interested here. Besides, the examination was, according to the authors, incomplete.

In my further discussion I will place in italics the doubtful cases, as those described by Redlich, Rossolimo, Walter, Henneburg i, Claude and Lhermitte, and Rochon-Duvignaud. The cases of Beneke and Heubner are so difficult to classify that I do not include them here.

Twenty-six cases are still left, of which those of Ceni and Cassirer and Lewy must be regarded as instances of blastomatosis. The remaining twenty-four I have divided into so-called inflammatory cases (A) and so-called degenerative cases (B).

A	B	C
Schilder ii.	Schilder i.	Ceni.
Jakob.	Marie and Foix.	Cassirer and Lewy.
Braun.	Hermel.	
Stauffenberg.	Klarfeld.	
Redlich.	Kaltenbach.	
Bouman i.	Krabbe.	
Rossolimo.	Bouman ii.	
Henneberg i.	*Walter.*	
Henneberg ii.	*Claude and Lhermitte.*	
Siemerling and Creutzfeldt.		
Schröder i.		
Schröder ii.		
Schröder iii.		
Neubürger		
Rochon-Duvignaud.		

I will now discuss in succession the gross lesions and the histological changes met with in these cases.

Both the right and left hemispheres were usually affected, but in some cases the one more than the other. In a few instances subcortical parts were also involved.

In some descriptions, moreover, it is impossible to decide accurately how far the disease extended. In nine cases in which we have exact

data the frontal lobes were less involved than the occipital lobes, whereas in seven cases it was just the reverse. In most cases lesions were found in both hemispheres, and these generally involved the corpus callosum as well as the frontal, temporal, parietal and occipital lobes. The occurrence of unaffected areas in the anterior and posterior central gyri was a conspicuous feature in many descriptions. Sometimes small isolated foci, apart from those which resembled patches of multiple sclerosis, could be seen which were to the naked eye apparently unconnected with the larger patches of disease.

As a rule the large ganglia were unaffected, but there were exceptions; both optic thalami were involved in Schilder's case ii, the nucleus caudatus on the left side in Jakob's case, the nucleus lentiformis and the optic thalamus in *Claude-Lhermitte's* case, and basal ganglia partly in Hermel's [8] case, the pons, medulla oblongata and cerebellum in Siemerling and Creutzfeldt's case, the corpus striatum and pes pedunculi in Schröder's case ii, [23] and finally the cerebellum in Kaltenbach's case [11].

In several instances the cortex was entirely normal, as in the cases described by Stauffenberg (only cellular increase here and there around the vessels), Marie and Foix, Kaltenbach, Krabbe [13], Bouman i, *Rossolimo, Henneberg* i, Henneberg ii, *Claude and Lhermitte* (in some places distention of vessels but no infiltration), Siemerling and Creutzfeldt Schröder ii, Schröder iii, and *Rochon-Duvignaud.*

In other cases the deepest cortical layer was involved, as in the cases of Klarfeld [12] (changes in the ganglion cells, proliferation of large glial cells and fibrous glia), Bouman ii (fifth and sixth layers, see description), Schröder i (occasional disappearance of myelin sheaths in the deepest cortical layer) and Neubürger (see later). Further, these changes varied in severity. In Schilder's case i there was a small patch of disease indistinctly demarcated from the neighbouring cortex, in which the ganglion cells were severely damaged, reticular glia and scavenger cells were present and the adventitial lymph sheaths were infiltrated. Considerable uncertainty exists with regard to Schilder's case ii. Schilder himself did not mention any cortical disturbances, but Haberfeld and Spieler discovered in the temporal and central lobes an almost complete absence of large pyramidal cells and a distinct decrease of the small and medium sized pyramids.

In Jakob's case there were areas of chronic degeneration and loss of ganglion cells and progressive glial changes in the deeper cortical layers. In some places where the cortex was damaged there were endarteritic

changes in the capillaries, a new formation and budding of vessels and emigration of lymphocytes, especially of plasma cells. The ganglion cells appeared as though torn, the nuclear membrane being no longer visible. There were scavenger cells also around the atrophic ganglion cells. Many cortical cells and some cells in the head of the caudate nuclei were in acute cloudy swelling. The glial elements were proliferated and rod cells were present.

In Braun's case the cortex of the left middle temporal gyrus contained a thick wall cyst the size of a pea, but the tissue around it was normal; its bottom was smooth and its wall white and firm. Even where no disease existed the cortex contained "monster" glial cells and sausage- and crescent-shaped fat-granule cells around the vessels.

Hermel's case exhibited disturbances in the structure of the cortex where the lesions were more severe; these consisted of acute ganglion cell changes. The Betz-cells were shrivelled, their nuclei stained darkly, their plasma was diffusely granular, and there were amœboid glial cells; the myelin sheaths were generally preserved. The cortical vessels were increased in number and there were hæmorrhages but no inflammatory changes.

In Walter's case the architectonic structure of the cortex was scarcely disturbed, but in places it was thinned and the number of ganglion cells reduced. In the left temporal lobe some cells had disappeared. The basal ganglia contained few scavenger cells but there was no degeneration.

In Neubürger's case there were in places at the bottom of the sulci disturbances in the deepest cortical layer, similar to those in the white matter (infiltrated vessels, &c.). The more superficial layers were compressed. The structure of the cortex above the area of disease was undisturbed but its cells were reduced in size, frequently presented a peculiar elongation, were generally indistinctly demarcated, stained faintly and metachromatically, and the perinuclear zone was pale and the rest crumbly or spongy. The Nissl substance had disappeared, or was scattered as fine granular matter round the borders of the cells. The prolongation of the cells often stained a dirty reddish colour. The nuclei were frequently not round and had changed their position; in some cells they had distinct, in others indefinite, membranes, and they were usually pale and delicately stippled or reticular in structure; the nucleolus was usually small and deeply coloured. In the deeper and middle layers of the cortex many cells also showed the acute Nissl-change, except in their coloured prolongations. In the

sixth layer there was an increase of satellite nuclei but no genuine neuronophagy. Finally, a small number of elements were also in a state suggesting more chronic change. The glia as a rule appeared to be in a state of active growth, as it contained large pale nuclei of dirty-reddish colour and irregularly demarcated plasma. No particular change was observed in the vessels.

The pia was usually normal where the cortex was not involved or where the sixth layer only was affected. In Schilder's first case the pia in the neighbourhood of the small cortical focus contained more scavenger cells than any other part, and in Jakob's case it was also infiltrated. In Braun's case the pia was thickened and contained numerous lymphocytes, fat-granule cells and proliferated glial fibres around the vessels in those regions where the disease almost reached the cortex, as in the right frontal lobe. In Hermel's case, on the contrary, the pia was unaffected. In the cases described by *Rochon-Duvignaud*, Neubürger, and Kaltenbach, and in Bouman's second case, the pia was thickened; no infiltration was present in the first three cases, but there was some in the fourth. In *Walter's* case too it was thickened and contained an increase of nuclei and scavenger cells; in *Henneberg's* first case it was infiltrated by a few scattered small mononuclear cells. In Siemerling and Creutzfeldt's case a patch of dense infiltration by macrophages, some of which had become scavenger cells, as well as polyblasts and lymphocytes, was found in the pia. There were also cells in the vessel walls, but plasma cells were rarely found.

Myelin sheaths.—On examining with the naked eye a section stained by the Weigert-Pal method, a striking change could be seen in the severely affected parts, but even here there was a remarkable preservation of the fibræ arcuatæ in most of the cases, though some of them might show signs of disintegration. But in many cases in which the fibræ arcuatæ were on the whole preserved places could be found in which they had disappeared, as in the cases of Jakob, Marie and Foix, *Walter*, Neubürger and in Schröder's third case. Sometimes they were preserved but obviously thinner than normal, as in Kaltenbach's case, or most of them were gone, though in places they were still visible, as in Hermel's and Schröder's first case. Finally, there were specimens in which the U-fibres were not at all affected, as in Klarfeld's case.

Both in Marie and Foix' and in *Walter's* cases it was stated that the fasciculus longitudinalis inferior passed unaffected through the focus, and in the first of these a few thin fibres of the thalamic radiations also crossed the diseased area. The reverse was found in *Rochon-Duvignaud's*

case, where the thalamic radiations were less well stained by the Weigert-Pal method than the surrounding tissues.

In Schilder's first case the remains of the myelin sheaths were rarely visible at the margin of the cortex, but were abundant in the vicinity of the ventricle; in *Rossolimo's* case a thin layer of myelinated fibres was present near to the walls of the ventricles, as well as a small number of the fibræ arcuatæ externæ.

Microscopical study showed that a few myelin sheaths could be stained in the grey areas, as in my first case and in the case of Siemerling and Creutzfeldt. In the latter, however, the stain on the one side was less deep and on the other varicose distentions, rosary-like irregularities and fragmentation of the fibres were visible.

In Kaltenbach's case, where the macroscopical changes were slight, many myelin sheaths were preserved. The continuity of these sheaths was frequently interrupted by distentions, sometimes on one side of the fibre only but generally on both sides, producing bizarre shapes. These distentions often succeeded each other in a row, only separated by short portions of myelin sheaths of normal breadth, or by very thin rings. As the disease progressed these thin junctions were broken through and the isolated masses remained lying in the tissue; in course of time they become more globular in shape. These globules, the distentions and the normal myelin sheaths were not equally darkly stained, and a number of spots, particularly close to the distentions, remained faint and unstained.

In Krabbe's case the myelin was on the whole well preserved, but around those vessels where there were perivascular proliferations of the glia the myelin sheaths had completely gone. In other places there was a diffuse atrophy of the sheaths, which Krabbe regarded as secondary. Here the adventitial lymphatics were packed with cells containing large amounts of granular protoplasm, which represented the disintegration products of the myelin sheaths.

In *Walter's* case the presence of thin fibres was mentioned, but there was no demarcation between the affected and the unaffected tissue; this was quoted as evidence against multiple sclerosis. In Schröder's second case too the boundaries between the diseased and healthy parts were indistinct.

The *axons* were but slightly affected in many cases; in others, on the contrary, but few remained. Between these extremes there were cases in which the axons were fairly preserved but had undergone considerable changes. They were better preserved than the sheaths;

their state, in fact, bore no relation to the amount of degeneration in the latter (cases of Braun, Stauffenberg, Klarfeld, Siemerling and Creutzfeldt, and Kaltenbach). In *Walter's* case, which was atypical in other respects, the number of axons was, however, reduced on the whole parallel with the disappearance of the myelin sheaths.

In my first case probably all the axons were preserved, but the greater part of them stained faintly by Bielschowsky's method; some of them, however, were impregnated more deeply and were irregular in size and occasionally varicose. In *Rossolimo's* case also the axons were almost without exception intact. In Schilder's first case slight axonal changes were observed; some had disappeared and others were distended, irregular in calibre, and undulating in the frontal and central lobes. In my second case many axons stained faintly, but a vastly greater number than in my first case stained well, though some had varicose distentions. In Schilder's second case some were intact and even perfectly straight, but in places, as in the parietal, occipital, and temporal lobes, there was a decrease in their number, and others showed evidences of degeneration. In Kaltenbach's case, too, sharply outlined elongated and globular swellings of the axons were described; these swollen fibres could be often traced for long distances.

Jakob records that in his case axons could be seen only here and there; in the vicinity of intensely infiltrated vessels they were generally absent, while farther from the vessels they were thin and showed evidences of degenerative changes. In areas of acute disease most of them, as a rule, had disappeared, and in the more chronic patches hardly any traces of nerve fibres were left. Here, too, the disappearance of myelin sheaths was, on the whole, greater than that of nerve fibres (compare Braun and others). In some patches where the myelin sheaths had gone the axons remained intact. Jakob also observed areas of disease, similar to patches of multiple sclerosis, in which the axons were entirely unaffected while the myelin sheaths had disappeared. In this case the vascular infiltrations were mainly slight, and the infiltrating cells showed but little tendency to leave the walls of the vessels.

In Marie and Foix' case but few axons persisted in the centres of the patches of disease and these were irregular, enlarged, beaded, and sometimes fragmented. In Neubürger's case a severe destruction of axons was observed, only a few well-preserved fibres being found at the periphery of the affected areas.

Secondary degeneration has been frequently described. In Schilder's first case Marchi's method revealed a degeneration of the right fasciculus

cerebro-spinalis and of the left fasciculus cerebro-spinalis anterior which was not visible in Weigert-Pal preparations. Marchi's method also showed degeneration in the posterior roots, and in his second case a secondary degeneration of the fasciculi cerebro-spinalis laterales and anteriores. This was also present in the cases recorded by Jakob, Marie and Foix, *Rossolimo*, Siemerling and Creutzfeldt, and to some extent in Schröder's first case. In neither of my cases was I able to examine the spinal cord, so that I could only determine the absence of degeneration in the brain-stem; it is possible there was pyramidal degeneration in the cord since Marie and Foix had observed little degeneration in the pons and cerebral peduncles, but a considerable amount in the spinal cord. In the olivary region of Marie and Foix' case the left pyramid was diminished in size and the right was small and sclerotic, but in the pons and in the peduncles the left pyramid was almost normal and the right somewhat increased in size. From this it appears that the most marked degeneration occurred farthest from the cells of origin of the cerebrospinal fibres. *Henneberg's* first case showed degeneration of the pyramidal tracts it is true, but it resembled that found in funicular myelitis; a large number of ganglion cells in a state of chronic degeneration were also found in the anterior horns. In his second case, on the contrary, there was no secondary degeneration. Schröder's second case showed secondary degeneration of the pyramidal tract in the pons and spinal cord, and in the pes pedunculi a band of secondary degeneration more mesially situated.

Blood-vessels.—Most contradictory statements are made as to the state of the blood-vessels in the various cases. One may say that the condition of the blood-vessels is of the greatest importance in classifying the cases into so-called inflammatory and purely degenerative types. My two cases may serve as examples. In the first the vessels were increased in number and in size. Their adventitial sheaths were densely infiltrated by cells, especially by lymphocytes, as well as by cells resembling degenerated plasma cells, a few "mast" cells, and finally scavenger cells, which were scarce in some places and abundant in others. Further, in the sheaths of the vessels oval nuclei similar to swollen endothelial nuclei, and large pale nuclei closely resembling those of "gemästete" glia cells, were found. The mesenchyma was also increased. On the other hand my second case showed no increase of vessels in the diseased area, and those present were not infiltrated, except close to the periphery of the lesion where a few connective tissue elements and some scattered lymphocytes were present in the widely meshed perivascular lymph spaces.

Jakob's case corresponds to my first case, the infiltration of the vessels consisting of lymphocytes, plasma cells and polyblasts; plasma cells were also found outside the vessels, and there were many small scavenger cells, partly of mesodermal, partly of glial origin. Every focus of disease of the myelin sheaths, whether acute or chronic, contained mesenchymal tissue, and there was severe endarteritis of the capillaries in the rare cortical patches. The same occurred in Braun's case, where lymphocytes, scavenger cells and a few leucocytes, but no plasma cells, lay in the perivascular spaces, while in the apparently unaffected surrounding tissue there was some infiltration, hæmorrhage and an increase of endothelial cells in the smaller vessels. In Stauffenberg's case dense collections of cells were present in the sheaths of the vessels, even in the apparently normal tissue. Siemerling and Creutzfeldt described a marked infiltration by plasma cells and lymphocytes in the adventitial spaces, and plasma cells freely scattered through the tissue close to the vessels, as well as scavenger cells and epithelioid elements rich in plasma (macrophages) in the sheaths of the precapillaries and veins; there was also an apparent increase of vessels, which is probably to be explained by the increase of cells in the walls of the veins and capillaries. In Neubürger's case there was also vascular infiltration by scavenger cells, plasma cells and lymphocytes, and fat-granule cells, often arranged in circles, were seen in the walls of the vessels. Plasma cells, mast cells, fat-granule cells and "gemästete" glial cells also lay in the very cellular tissue between the vessels. Where the products of degeneration had disappeared the vessels were infiltrated and the mesenchyma had increased. In the centre of the patches alternate masses of glial fibres and mesenchymal fibres were found. Schröder's cases and Henneberg's second case may be included in the inflammatory type. Schilder's second case also belongs to this group since it showed chiefly lymphocytic infiltration of the vessel sheaths, but no plasma cells, polyblasts, or scavenger cells peripherally to the lymphocytes; the vessels in the neighbourhood of the disease were infiltrated, and there was congestion of the lymph spaces around many vessels. In Schilder's first case the process was purely degenerative, but there was an infiltration by scavenger cells, lymphocytes, or the small lymphocytes of Held, and occasionally a slight proliferation of the intima and adventitia of the vessels. The disease was similar in Marie and Foix' case, but there was no perivascular infiltration, and only slight proliferation of the sheaths of the vessels. Hermel's case also showed no infiltration, although there were scavenger cells in the

vessel walls, accumulations of small glial elements, an increase of vessels, new capillary formations and fresh hæmorrhages. In both the cases of Klarfeld and Kaltenbach it is stated that there was hardly any vascular infiltration. Krabbe's case exhibited dense masses of cells around the vessels, it is true, but they consisted of glial elements, some being rich in protoplasm, others granular and without formed fibres.

The brief descriptions available leave us in doubt as to the nature of the cases described by *Redlich*, in which there was lymphocytic infiltration of the vessels in and around the diseased area; by *Rossolimo*, who speaks of leucocytic infiltration, scavenger cells, fat droplets, hyperplasia of the endothelial nuclei and increase of vessels; and by *Henneberg* (first case) where some large vessels were infiltrated by small cells, which in the pons and medulla oblongata extended into the surrounding tissues. Many leucocytes were observed in the insufficiently examined case of *Rochon-Duvignaud*, who regarded them as a lymphocytic infiltration.

These cases may be placed in the inflammatory group, but other cases, as *Walter's*, in which the perivascular infiltration in the white matter consisted of glial nuclei, scavenger cells and occasionally lymphocytes, may rather be classed with the degenerative forms. In *Claude and Lhermitte's* case there were small accumulations of lymphocytes around some vessels and scattered hæmorrhages.

In *Ceni's* case, one of the two of the blastomatosis type, dilated lymph spaces containing small and large nuclei, apparently belonging to lymphocytes undergoing degenerative metamorphosis, were found around the arteries. In *Cassirer and Lewy's* case, on the other hand, no infiltration was found.

Glia.—Jakob's case may be taken as typical as regards the changes in the glia. Here the parts rich in fibres, which may be regarded as representing scar tissue, were poor in glial cells. In the older patches of disease a dense "gliafilz" was present, but the proliferation of the glial cells extended far beyond the limits of the disease. Giant glial cells were also found in the margins of the affected areas and even in the neighbouring white substance where there were no severe degenerative changes. The large "gemästete" glial cells seemed to bear little relation to the destruction. Neubürger's case was very similar to Jakob's.

In suitably stained preparations it appeared that many "gemästete" glial cells were forming fibrils; they were often surrounded by smaller glial cells, by which it seems they may be replaced. Much-twisted

glial fibrils of various sizes which radiated in every direction developed from the protoplasmic processes of the cells. In the centre these coalesced into a compact basket-work and here the number of the large glial cells was diminished. The central portions of the affected areas were occupied by proliferating glial fibrils, the younger elements of which consisted of numerous astrocytes and firm but not very dense masses of fibrils, whereas the older areas were poor in nuclei and contained compact bands of more delicate fibrils. This was the condition found in my first case. In Siemerling and Creutzfeldt's case there was a marked increase of glial elements of various forms, "Gittercells" (scavenger cells staining by Nissl's method), giant glial cells, "gemästete" glial cells, as well as developing and regressive glial elements. Fat stains revealed the scavenger cells more distinctly. Some cells contained small granules up to fifteen in number, certain of which resembled developing nuclei; others possessed not more than one or two chromatin globules, while others were pale and empty so that they looked like shadows. Rod cells were found almost without exception, and there were loose glial nuclei and the epithelioid glial cells with more or less developed, metachromatically staining bodies.

Schilder's second case had a certain resemblance to these cases. There was an increase of cells, large glial cells rich in plasma, a moderate number of scavenger cells and glial cells of the normal type. A dense glial tissue had also developed. The large glial cells assumed less strange shapes than Schilder's first case, and their nuclei possessed well-developed chromatin meshworks. In the occipital region, however, irregularly-shaped nuclei were seen. Cells with four or five nuclei were not uncommon. Fat-granule cells were rare in the occipital region only.

In Braun's case there was an increase of fat-granule cells towards the centre of the disease; in the periphery the development of scavenger cells could be traced from proliferating glial elements. There were probably fat droplets in the processes of the glial elements. An abundance of giant glial cells showing amitotic karyorexis were found intermingled with glial nuclei. Sausage- and crescent-shaped giant glial cells were also present.

In cases where no definite mention has been made of the state of the glia, large cells rich in protoplasma with blurred outlines and indistinct nuclei were always described, or reference was made to fat-granules free or in cells; to spider-shaped glial cells with numerous coarse processes (Stauffenberg); to large glial cells and an abundance of glial

fibres (*Redlich*); to glial nuclei in the vicinity of the vessels, glial overgrowth and scavenger cells (Henneberg ii); to scavenger cells, proliferating glial elements, large glial cells and glial fibrils (Schröder i); to scavenger cells, "giant" glial cells and glial fibrils (Schröder ii); to "giant" glial cells and glial fibres in the reticulum of the glial cells; or to a few scavenger cells (Schröder iii) in the centres of areas of intense glial proliferation; or to a delicate reticulum filled with large astrocytes (*Rochon-Duvignaud*).

In Marie and Foix' case there were more fibrils than cells in the old sclerotic areas, and close to their centres hardly anything but delicate fibrils. In Hermel's case there were small elements with round, often pycnotic, nuclei interspersed with large pale glial cells, as well as giant cells and an abundance of scavenger cells. In Klarfeld's case reticular and cellular increase, "gemästete" glial cells and fibrous glia in the demyelinated regions were described. In Krabbe's case an increase of glial cells rich in protoplasm, the nuclei being situated peripherally, is described in addition to the ordinary spider-cells and glial cells showing transitions from normal to pathological forms. In my second case the glial cells were smaller than in my first case, and there were scavenger cells with little fat and many glial fibrils. In *Walter's* case large scavenger cells, astrocytes, and an increase of glial fibrils are described. In *Claude and Lhermitte's* case astrocytes and "giant" glial cells were found in the centrum ovale, in addition to thick glial fibrils. There was also proliferation of the neuroglia in the lenticular and caudate nuclei, in the optic thalamus, in the internal capsule, and in the corpus callosum.

Kaltenbach definitely states that in his case there was little reaction in the neuroglia, there being few glial cells and fibrils, and rarely any evidence of the formation of fibrils by the glial cells.

Finally, in Schilder's first case large glial cells, some of which were producing fibres, many fat-granule cells and glial fibrils are described. Kaltenbach found peculiar products, which were also seen by Siemerling and Creutzfeldt and in my second case. In this case various stages in the development of scavenger cells were observed; they did not give any fat reactions.

If we review the various macroscopical and microscopical findings with special attention to what they have in common, we arrive at the following results:—

Macroscopically the chief and most conspicuous feature is the wide-

spread affection of the white matter of both hemispheres. The colour of the diseased areas varies from grey, greyish-red to yellow; their consistency may be either firm, gelatinous or spongy. To the naked eye the lesions appear sharply demarcated and the configuration of the brain is preserved. Microscopical examination showed in some cases signs of inflammation with alteration, exudation and proliferation, while in others there was a marked resemblance to the changes of the so-called degenerative myelitis.

The differences between these two types must probably be sought in the intensity of the virus and the more or less violent reaction of the tissues. The preservation of the fibræ arcuatæ, or perhaps more correctly of the fibres immediately under the cortex, is peculiar; it is, however, analogous to the condition found in thrombosis of the vessels of the white matter and in arterio-sclerotic affections of the long central medullary vessels. It may be that the pathological agent reaches the white matter of the hemispheres along the blood-vessels and here involves the myelin sheaths and the axons. Then extending in various directions it eventually involves the whole centres of the hemispheres, but is arrested on reaching the fibræ arcuatæ. It is true, however, that higher magnification showed, in my case at least, that even these had not escaped completely, and also revealed changes in the fifth and sixth cortical layers. The fact that there were in my second case lesions in the fibræ arcuatæ and in the sixth cortical layer also indicates that the fibræ arcuatæ do not form an absolute frontier line.

Particularly characteristic in the histopathological examination are the "gemästete" glial cells surrounded by elements which are probably of a phagocytic nature.

Our attention is next arrested by the exudative-infiltrative changes which cannot be considered as "secondary inflammatory reactions" (Spielmeyer), since the infiltrations are certainly not dependent on the intensity of the degenerative lesions in the parenchyma. The mesenchymal proliferation originating from the vessels is also remarkable. Finally, the dense masses of glial fibrils and the giant glial cells are striking features.

Secondary degeneration has as a rule not been observed in the brain-stem, though some exceptions have been noted. In several cases small foci, similar to those of multiple sclerosis, were present. This emphasizes the close relation between the pathological process in this disease and that in multiple sclerosis. Inflammatory changes starting around the blood-vessels and glial-scars are found in both.

There can be no question of the similarity in the clinical pictures of the disease in all the cases so far recorded. The process may start at different places in the white matter, now leaving one part, now another unaffected; it may occasionally affect the cortex, the pia may exhibit changes, and we consequently find varying groups of symptoms dependent on the special localization of the disease. Further, it may be assumed that the disease attacks fibres of certain functions more virulently than others; for instance, sensibility is undisturbed though large areas of the hemispheres are demyelinated. Unfortunately, several patients could not be sufficiently observed before their admission to hospital, so that the record of the symptoms then present is very incomplete or absent. For example, Jakob's patient was found in a morbid state and was not able to give any history. The psychical conditions of several patients were often such as to render the examination of sensation uncertain, and generally to leave much to be desired in the investigation of disturbances of speech; consequently it is often necessary to rely on doubtful records. Even where the examination of vision could be carried out difficulties arose as a result of the lethargy of the patients.

The diagnoses generally made were either multiple sclerosis, cerebral tumour, or "organic disease of the brain." Stauffenberg's first case was first regarded as multiple sclerosis aud afterwards as a diffuse encephalitis akin to multiple sclerosis. The fourth diagnosis in Oppenheim-Henneberg's case was cerebral tumour, the fifth disseminated encephalitis, the sixth acute multiple sclerosis. (The first diagnosis had been hysteria, the second polyneuritis, the third tubercular spondylitis.) Twice, in Kaltenbach's and *Walter's* cases, the diagnosis of dementia paralytica was made; in the latter it was changed to diffuse sclerosis of the brain. Once, in Krabbe's case, tuberculous meningitis was diagnosed, but tetany was also considered. Sometimes only a more indefinite diagnosis was made, as a compressing lesion, probably in the posterior cranial fossa, in the case of blastomatosis described by *Cassirer and Lewy*. Neubürger's case was regarded as a doubtful tuberculous affection of the brain. *Claude and Lhermitte's* case, which in all likelihood did not belong to our group, was diagnosed as central encephalitis involving chiefly the centrum ovale and corpus callosum, whereas one of Schröder's cases was supposed to be an infiltrating sarcomatous tumour.

A tumour was localized in the posterior cranial fossa in Schilder's first case; in the right occipital lobe in my first case, and in the

cerebellum, spreading into the pons and medulla, in one of Schröder's cases. Ceni's case, which belonged to the blastomatosis type, was diagnosed as a glioma. No diagnosis was made in Klarfeld's case, in my second case, in Siemerling and Creutzfeldt's case, nor in Schröder's two cases.

This review clearly shows that the symptoms are so variable that it is even impossible to discover an approximate unity in the diversity. A glance at the different localizations which have been made is quite sufficient to show that we pass the limits of diagnostic possibility in this very characteristic structural disease. The prominence of general symptoms naturally raises the suspicion, in the first place, that one of the more common brain affections exist, the very rare disease with which we are concerned not being taken into consideration. It is very rarely that clinicians have ventured to think of it. Further, it is scarcely ever possible to determine the direction in which the process extends. Thus, Jakob believed that in his case the disease spread from in front backwards, the starting point being assumed to be in the central gyrus, since an epileptiform Jacksonian attack followed by hemiparesis was the first symptom. Schilder states emphatically that there are no clinical indications of where the lesion commences, though it seems probable that in his first case the left hemisphere was affected before the right.

The symptoms of the different cases may be arranged in tabular form, as it is easier to orientate oneself in a table than in a longer description. Sometimes for the sake of space only a brief extract has been given; the details of my own cases will be found in the preceding pages. In the table one can see that general symptoms such as headache, vomiting, incontinence and fatigue, were found in the majority of the cases, though in some the absence of general symptoms is mentioned. The mind was usually affected, which is not surprising in such a diffuse process; apathy is most frequently recorded, but disorientation, forgetfulness, euphoria, crying and screaming are also included. In a few instances, however, the mental condition had not suffered.

The occurrence of other cerebral symptoms is surprisingly uncommon. Epileptiform attacks, except in the blastomatosis case of Cassirer and Lewy, occurred only in my two cases (especially in my second case), in Siemerling and Creutzfeldt's case, in Klarfeld's and in Neubürger's cases. Choked optic discs were observed only in a minority of the cases, and temporal atrophy of the disc was an exception.

Spastic paralysis and contractures affecting the arms and legs together or separately, or mainly one side, and alternating between the right and the left sides, were of rather frequent occurrence.

Walking was often impossible even in the early stages (one-fifth of the cases), or the gait was stumbling and unsteady. The feet were, in my second case and in four other cases, in the equinovarus position and in four cases the legs were crossed.

Tonic and clonic convulsions, which may be regarded as irritative phenomena, occurred respectively in four and seven cases, and turning of the head and (or) eyes towards one side in five cases.

The pupils were slightly sluggish to light in four cases, in four there was (sometimes temporary) anisocoria, and mydriasis is described in four other cases; in *Rochon-Duvignaud's* case it was combined with Argyll Robertson's sign. A good reaction was, however, frequently observed, but in some instances the condition of the patient probably did not permit a careful investigation of the pupillary reflexes. In Ceni's blastomatosis case the pupils did not react, and in Cassirer and Lewy's the right pupil gave no reaction to light and was not round; in Neubürger's case also the pupils did not react to light.

Disturbances of the ocular muscles were found in a little less than half of the cases, usually in the form of strabismus, diplopia, disturbance of the conjugate movements, and, in one patient, ptosis. A slight nystagmus was observed in a limited number of the cases, but it was usually only transitory or present in extreme position of the bulbs.

Hemianopsia occurred in addition to my cases in three other instances; in some patients scarcely any vision remained, or the fields of vision were much contracted. In *Rochon-Duvignaud's* case sudden blindness occurred, and this also developed in Stauffenberg's case towards the end of the illness. Mutism was frequently found, being either of psychic origin or not. Sometimes there was aphasia, dysarthria or echolalia. Occasionally slight traces of apraxia were present.

Unilateral facial disturbances were noted in ten cases; the hypoglossal nerve was occasionally affected, and trismus and buzzing in the ears have been also recorded.

Exaggerated knee- and Achilles-jerks, and frequently clonus, were found in a large majority of cases; there were occasionally differences between the two sides. In some cases there was an alternation between clonus and absent reflexes. The Babinski reflex was often present, either on both sides or on one side only; sometimes it appeared only after an attack, but it was generally present independently of attacks.

Cases	Sex and age	Duration of illness	General symptoms	Psychical symptoms	Disorders of vision	Optic discs
Schilder i	F. 14	4½ months	Headache, vomiting ..	Apathetic, noisy ..	Much diminished, fields contracted, mainly for colours	Bilateral neuri
Schilder ii	M. 7	2 years	Headache, incontinence	Apathetic, noisy ..	Disturbances of vision	Normal ..
Jakob	M. 30	1½ ,,	Incontinence	Apathetic, disoriented	—	—
Braun	F. 39	?	Headache, incontinence	Apathetic	Hemianopsia	Normal ..
Ceni	M. 9	7 months	Headache, incontinence	Apathetic	—	Temporal ma pale
Stauffenberg	F. 21	8 ,,	Vomiting..	Emotional	Finally blind	Neuritis. L. poral margin
Marie and Foix	F. 28	10 years	—	Absent	Absent	—
Hermel	F. 4	17 months	Incontinence	Apathetic	—	Normal ..
Redlich	F. 41	12 ,,	Headache	Apathetic, forgetful ..	Hemianopsia	Neuritis ..
Klarfeld	F. 23	12 ,,	Headache, fatigue, vomiting	Forgetful	,, ...	Normal ..
Kaltenbach	M. 24	1¼ years	Incontinence	Euphoric	—	—
Krabbe	M. 1	5 days	—	Apathetic	-	Dubious ..
Bouman i	F. 32	6 months	Headache, vertigo, vomiting, slow pulse	Euphoric	Hemianopsia, acuity diminished	Bilateral neur
Bouman ii	M. 20	5 ,,	—	Emotional, noisy ..	—	—
Rossolimo	M. 16	12 ,,	Absent	Emotional	—	Normal ..
Walter	M. 40	3½ years	Absent	Apathetic, childish, depressed, confused	—	Normal ..
Heubner	M. 4½	1 year	Vomiting	—	—	Bilateral ne incipient atr
Henneberg i	M. 39	8—9 months	Incontinence	Disoriented, forgetful	—	Bilateral neur
Henneberg ii	F. 43	7 months	Fatigue	—	—	Normal ..
Claude and Lhermitte ..	M. 19	17 ,,	Vomiting, incontinence	Disoriented, forgetful, delusions	Vision diminished ..	Normal ..
Cassirer and Lewy ..	F. 37	9 ,,	Pressure symptoms ..	—	Vision diminished, fields contracted	Bilateral neu
Siemerling and Creutzfeldt	M. 7	2 ,,	—	Excited	—	Normal ..
Schröder i	M. 25	6 ,,	Fatigue	Apathetic	—	—
Schröder ii	M. 10	—	Absent	—	—	Temporary ne L.
Schröder iii	M. 12	2½ years	Incontinence	Apathetic, noisy ..	—	—
Neubürger	M. 12	Some days	Incontinence	—	—	—
Rochon-Duvignaud ..	F. 22	2½ months	Headache, incontinence	Absent	Rapidly blind ..	Bilateral neu

	Disorders of vision	Optic discs	Ocular movements	Pupils	Disorders of speech	Paralyses, contractures and tremors	Tendon reflexes	Plantar reflex	Abdominal reflexes	Sensatio
..	Much diminished, fields contracted, mainly for colours	Bilateral neuritis ..	L. vi, paresis, slight nystagmus	—	Anarthria, later mute ..	Spastic R. hemiplegia after operation	—	R. ↑	—	—
..	Disturbances of vision	Normal	Affected	Reactions sluggish ..	Aphasia	Bilateral paralysis and contractures; pes equinovarus, intention tremor	Knee and ankle clonus	R. ↑ L. ↑	—	Pain diminis
ed	—	—	Disturbances in looking up and to R.	Unequal after attacks ..	Mutism	R. hypertonia after attacks ..	Knee and Achilles jerks exaggerated	—	O	—
..	Hemianopsia	Normal	—	—	Slight apraxia	Triplegia, L. vii, paresis ..	Triceps jerk R. > L., knee and Achilles jerks exaggerated	After scopolamine injection ↑	—	—
..	—	Temporal margins pale	Eyes deviated to R. Nystagmus 4 months after onset	Dilated, reactions lost ..	Scanning speech, mutism	Bilateral paralysis and contractures, mainly R.; pes equinovarus, intention tremor	Arm jerks R. > L., knee and ankle clonus	—	Diminished	Pain diminis
..	Finally blind	Neuritis. L. temporal margin pale	Eyes deviated to L. Horizontal nystagmus	—	—	Fine tremor of hands	Knee and Achilles jerks exaggerated, crossed adductor reflex from R.	R. ↓ later ↑, L. ↑	R. diminished L. O	—
..	Absent	—	Slight squint	—	Aphasia ?	Quadriplegia, afterwards triplegia. Pes equinovarus	Knee and Achilles jerks exaggerated, mainly L.	R. ? L. ↑	—	Intact ..
..	—	Normal	Slight horizontal nystagmus	—	Able to understand, did not speak	—	Knee and ankle clonus	R. ↑ L. ↑	O	Intact ..
..	Hemianopsia	Neuritis	R. vi paresis	—	—	L. hemiparesis	—	—	—	Hemianæsthe
..	, ...	Normal	—	—	Motor aphasia, mainly after attacks	R. spastic paresis after attacks ..	Ankle clonus	R. ↑	—	—
..	—	—	—	Unequal, irregular, reactions sluggish	Slight scanning	Fine tremor of hands	All exaggerated	—	—	Intact ..
..	-	Dubious	Convergent strabismus. R. ptosis	Reactions sluggish ..	—	Alternately hyper- and hypotonia in different regions	—	R ↑ L. ↑	—	—
..	Hemianopsia, acuity diminished	Bilateral neuritis ..	Normal	Normal	Normal	See text	Achilles jerk R. > L.	L. ? after attack	Lower diminished	Intact ..
..	—	—	Conjugate deviation first to R., later to L.	Dilated	Echolalia, later mutism ..	See text. Pes varus	Knee and Achilles jerks exaggerated, L. > R., afterwards Achilles jerk normal	R. ↑ later R. ↓ L. ↓	O	Hyperasthesia leg
..	—	Normal	Bilateral vi, and R. iii paresis. Slight nystagmus	Reactions sluggish ..	Progressive dysarthria ..	R. spastic paralysis	Knee and Achilles jerks exaggerated	—	—	Tactile dimi
h, d	—	Normal	—	Reactions normal	Aphasia, alexia, agraphia, apraxia	Spastic paralysis of legs	Knee and Achilles jerks exaggerated, afterwards clonus	R. ↓ L. ↓ later R. ↑ L. ↑	Before death O	—
	—	Bilateral neuritis, incipient atrophy	—	Reactions normal	Lisping	Spastic quadriplegia, pes equinovarus, fine tremors of the hand, often intention tremors	Knee jerks exaggerated	—	—	Intact .
ful	—	Bilateral neuritis ..	Diplopia, transient nystagmus	Reactions normal	Dysarthria	—	Temporary clonus	R. ↑ L. ↑	O	R. anæsthesia hypalgesia
	—	Normal	Diplopia, R. vi, paresis, nystagmus	Anisocoria	Progressive loss	L. hemiplegia, R. vii, paresis ..	Knee and Achilles jerks exaggerated	R. ↓ L. ↑	L. O R. +	Disturbances I cept in face
ul,	Vision diminished ..	Normal	—	—	Alternately apraxia, aphasia, mainly after elevation of temperature	Contracture of legs, later of arms	Arm, knee and Achilles jerks lost, afterwards exaggerated	R. ↑ L. ↑	Lower O	—
	Vision diminished, fields contracted	Bilateral neuritis ..	—	R. irregular, reactions lost	—	-	—	—	—	—
..	—	Normal	—	Reactions normal	Monosyllabic	Spastic paralysis and contractures of limbs, pes equinovarus	Knee and ankle clonus	R. ↑ L. ↑	Almost lost	—
..	—	—	—	—	—	L. leg paralysed	—	—	—	—
	—	Temporary neuritis, L.	Loss of deviation to R.	—	Bulbar, afterwards mute..	Static ataxia and adiadochokinesis R. hand, chorea, afterwards contractures	Knee jerk exaggerated	R. ↑, later both ↑	—	—
..	—	—	—	—	—	Spastic triplegia and contractures	—	R. ↓ L. ↓	—	—
	—	—	Normal	Temporary anisocoria, dilated, reactions absent	—	—	-	R. ↑ L. ↑ during attacks	—	—
..	Rapidly blind ..	Bilateral neuritis ..	—	Dilated, Argyll-Robertson	Disorders during attacks..	—	Knee jerk exaggerated, afterwards normal	R. ↑ L. ↑	—	Hyperæsthesia

	Paralyses, contractures and tremors	Tendon reflexes	Plantar reflex	Abdominal reflexes	Sensation	Epileptic attacks and spasms	Wassermann		C.S.F.		
							Serum	C.S.F.	Globulin	Cells increase	Pressure
e ..	Spastic R. hemiplegia after operation	—	R. ↑	—	—	—	+	?	+	—	—
..	Bilateral paralysis and contractures; pes equinovarus, intention tremor	Knee and ankle clonus	R. ↑ L. ↑	—	Pain diminished ..	Tonic and clonic spasms..	O	—	O	O	—
..	R. hypertonia after attacks ..	Knee and Achilles jerks exaggerated	—	O	—	Epileptiform attacks, tonic and clonic spasms	—	—	O	O	—
..	Triplegia, L. vii, paresis ..	Triceps jerk R. > L., knee and Achilles jerks exaggerated	After scopolamine injection ↑	—	—	—	—	—	+	—	O
utism	Bilateral paralysis and contractures, mainly R.; pes equinovarus, intention tremor	Arm jerks R. > L., knee and ankle clonus	—	Diminished	Pain diminished ..	—	—	—	—	—	—
	Fine tremor of hands	Knee and Achilles jerks exaggerated, crossed adductor reflex from R.	R. ↓ later ↑, L. ↑	R. diminished L. O	—	Epileptiform attacks, tonic and clonic spasms	O	O	+	+	O
..	Quadriplegia, afterwards triplegia. Pes equinovarus	Knee and Achilles jerks exaggerated, mainly L.	R. ? L. ↑	—	Intact	—	—	—	—	—	—
did not	—	Knee and ankle clonus	R. ↑ L. ↑	O	Intact	—	O	O	O	O	—
	L. hemiparesis	—	—	—	Hemianæsthesia L.	—	—	—	—	—	—
mainly	R. spastic paresis after attacks ..	Ankle clonus	R. ↑	—	—	Convulsions in the hand, eyes to R., blepharospasm, clonic spasms R. shoulder	—	—	—	—	—
..	Fine tremor of hands	All exaggerated	—	—	Intact	—	—	—	—	—	—
	Alternately hyper- and hypotonia in different regions	—	R ↑ L. ↑	—	—	Tonic and clonic spasms..	—	—	—	—	—
..	See text	Achilles jerk R. > L.	L. ? after attack	Lower diminished	Intact	R. clonic spasms	O	O	+	O	+
ism ..	See text. Pes varus	Knee and Achilles jerks exaggerated, L. > R., afterwards Achilles jerk normal	R. ↑ later R. ↓ L. ↓	O	Hyperasthesia R. leg	Head and eyes to R. Large movement with the R. arm (see text)	—	—	—	—	—
ia ..	R. spastic paralysis	Knee and Achilles jerks exaggerated	—	—	Tactile diminished	R. clonic spasms	—	—	—	—	—
raphia,	Spastic paralysis of legs	Knee and Achilles jerks exaggerated, afterwards clonus	R. ↓ L. ↓ later R. ↑ L. ↑	Before death O	—	—	—	O	O	O	—
..	Spastic quadriplegia, pes equinovarus, fine tremors of the hand, often intention tremors	Knee jerks exaggerated	—	—	Intact . ..	—	—	—	—	—	O
..	—	Temporary clonus	R. ↑ L. ↑	O	R. anæsthesia and hypalgesia	—	—	—	—	—	—
..	L. hemiplegia, R. vii, paresis ..	Knee and Achilles jerks exaggerated	R. ↓ L. ↑	L. O R. +	Disturbances L. except in face	—	—	—	—	—	—
apha- evation	Contracture of legs, later of arms	Arm, knee and Achilles jerks lost, afterwards exaggerated	R. ↑ L. ↑	Lower O	—	—	—	—	O	O	+
	—	—	—	—	—	Epileptiform attacks ..	O	—	—	—	—
..	Spastic paralysis and contractures of limbs, pes equinovarus	Knee and ankle clonus	R. ↑ L. ↑	Almost lost	—	Epileptiform attacks ..	—	—	—	—	—
	L. leg paralysed	—	—	—	—	Five epileptic attacks in three years	O	O	—	+	—
nute..	Static ataxia and adiadochokinesis R. hand, chorea, afterwards contractures	Knee jerk exaggerated	R. ↑, later both ↑	—	—	—	—	—	+	+	—
	Spastic triplegia and contractures	—	R. ↓ L. ↓	—	—	—	O	O	—	—	—
	—	—	R. ↑ L. ↑ during attacks	—	—	Acute status epilepticus with Jacksonian type attacks	O	—	—	16	—
acks..	—	Knee jerk exaggerated, afterwards normal	R. ↑ L. ↑	—	Hyperæsthesia ..	R. tonic spasms	O	O	—	—	+

The abdominal reflexes were absent in five cases, in three cases they were feeble, and in two absent on the one side and present on the other.

Intention tremor was twice recorded.

Sensation, as far as it could be investigated, was disturbed in a number of cases, but in a few only was there anæsthesia or hypalgesia.

The pressure of the cerebrospinal fluid was increased in certain cases (three out of six); only a small quantity of globulin and a small number of cells were found in some of the cases. As far as can be determined the duration of the illness in twenty-one cases was under two years, but in four cases it was longer. The ages of the patients varied between 1 and 43 years.

REFERENCES.

[1] Beneke. "Ein Fall hochgradigster und ausgedehnter diffuser Sklerose des Zentral, nervensystems," *Arch. f. Kinderheilk.*, 1908, **47**, 420.

[2] Braun. "Ueber ein Fall von diffuser Encephalomyelitis," *Zeit. f. d. ges. Neur. u. Psych.*, 1922, **80**.

[3] Cassirer und Lewy. "Die Formen der Glioblastose und ihre Stellung zur diffusen Hirnsklerose," *Zeit. f. d. ges. Neur. u. Psych.*, 1923, **81**, 290.

[4] Ceni. "Ueber einen interessanten Fall gliomatöser Infiltration beider Grosshirnhemisphären," *Arch. f. Psych. u. Nervenkrank.*, 1896, **31**, 809.

[5] Claude et Lhermitte. "Leuco-encéphalite subaigüe à foyers successifs," *L'Encéphale*, 1920, **15**, 89.

[6] Haberfeld und Spieler. "Zur diffusen Hirn-Rückenmarkssklerose im Kindesalter," *Deutsch. Zeitschr. f. Nervenheilk.*, 1910, **40**, 436.

[7] Henneberg. "Ueber disseminierte Encephalitis," *Neurol. Centralbl.*, 1916, **35**, 652, 984.

[8] Hermel. "Ueber einen Fall von Encephalomyelomalacia chronica diffusa bei einem vierjährigen Kinde," *Deutsch. Zeitschr. f. Nervenheilk.*, 1921, **68-69**, 338.

[9] Heubner. "Ueber diffuse Hirnsklerose," *Charité-Annalen*, 1897, **22**, 298.

[10] Jakob. "Zur Pathologie der diffusen infiltrativen Encephalomyelitis in ihren Beziehungen zur diffusen und multiplen Sklerose," *Zeitschr. f. d. ges. Neur. u. Psych.*, 1915, **27**, 290.

[11] Kaltenbach. "Ueber einen eigenartigen Markprocess mit metachromatischen Abbauprodukten bei einem paralyse-ähnlichen Krankheitsbild," *Zeitschr. f. d. ges. Neur. u. Psych.*, 1922, **75**, 139.

[12] Klarfeld. "Zur Frage der subakut verlaufenden diffusen Erkrankungen des Hemisphärenmarkes," *Allg. Zeitschr. f. Psychiat.*, 1922-23, **79**, 294.

[13] Krabbe. "Beitrag zur Kenntnis der Frühstadien der diffusen Hirnsklerose," *Zeitschr. f. d. ges. Neur. u. Psych.*, 1913, **20**, 108.

[14] Marburg. "Die multiple Sklerose," "Handb. der Neurologie," Lewandowski.

[15] Marie et Foix. "Sclérose intracérébrale centrolobaire et symétrique," *Revue Neurol.*, 1914, **27**, 1.

[16] Neubürger. "Histologisches zur Frage der diffusen Hirnsklerose," *Zeitschr. f. d. ges. Neur. u. Psych.*, 1921, **73**, 336.

[17] Redlich. "Demonstration eines Hirntumors mit regressiven Erscheinungen," *Wien. klin. Wochenschr.*, 1913, **26**, 82.

[18] Rochon-Duvignaud, Jumentié et Valière Vialeix. "Cécité à marche rapide avec stase papillaire modérée, mort dans le coma avec contractures intenses et généralisées. Foyers multiples d'encéphalite intéressant les radiations optiques." Société de Neurologie, séance du 5 juillet, 1923, *Revue Neurol.*, **30**, **ii**, 73.

[19] Rossolimo. "Zur Frage über die multiple Sklerose und Gliose," *Deutsch. Zeitschr. f. Nervenheilk.*, 1897, **11**, 88.
[20] Schilder i. "Zur Kenntnis der sog. diffusen Sklerose (über Encephalitis periaxialis diffusa), *Zeit. f. d. ges. Neur. u. Psych.*, 1912, **10**, 1.
[21] Schilder ii. "Zur Frage der Encephalitis periaxialis diffusa (sog. diffuse Sklerose), *Zeitschr. f. d. ges. Neur. u. Psych.*, 1913, **15**, 359.
[22] Schmaus. "Zur Kenntnis der diffusen Hirnsklerose," *Virchow's Archiv*, 1888, **114**, 1521.
[23] Schröder. "Encephalitis und Myelitis," *Monatschr. f. Psych. u. Neur.*, Bd. **43**, 146. Schröder iii nach den Demonstrationen von Bonhoeffer, *Neurol. Centralbl.*, 1912, **31**, 1048; *ibid.*, 1914, **33**, 986.
[24] Siemerling und Creutzfeldt. "Bronzekrankheit und sklerosierende Encephalomyelitis," *Arch. f. Psychiat.*, 1923, **68**, 217.
[25] Spielmeyer. "Histopathologie des Nervensystems," Berlin, 1922.
[26] Stauffenberg. "Ein Fall von Encephalitis periaxialis diffusa," *Zeitschr. f. d. ges. Neur. u. Psych.*, 1913, **39**, 556.
[27] Strümpell. "Ueber diffuse Hirnsklerose," *Arch. f. Psychiat.*, 1879, **9**, 268.
[28] Walter. "Zur Symptomatologie und Anatomie der diffusen Hirnsklerose," *Monatschr. f. Psych. u. Neur.*, 1918, **44**, S. 87.
[29] Weiss. "Ueber diffuse Sklerose des Hirns und Rückenmarks," *Obersteiner's Arb. a. d. neurol. Inst. a. d. Wien*, 1900, **7**, 245.

THE ENCEPHALITIS PERIAXIALIS OF SCHILDER. A CLINICAL AND PATHOLOGICAL STUDY, WITH AN ACCOUNT OF TWO CASES, ONE OF WHICH WAS DIAGNOSED DURING LIFE.

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SINCE Schilder in 1912 separated out from among the several conditions which had been reported as "diffuse sclerosis" of the brain, a pathological entity which he quite rightly considered to be an especial disease of itself and which he named "encephalitis periaxialis," twenty cases have been reported as corresponding with his description.

These cases have come to light upon post-mortem examination, but none of them were diagnosed clinically and even recent writers upon this subject have expressed their opinion that no clinical picture can as yet be drawn which will prove reliable for the diagnosis of this disease during life.

In 1902 a case occurred in the National Hospital under the care of Dr. Beevor which was carefully examined both clinically and pathologically by one of us. It bore the diagnosis of "progressive post-natal diplegia with blindness," but on pathological examination it was at once recognized as a condition entirely unknown in our experience. Elaborate photographic records of the pathological picture were made, and this case, though it occurred ten years before Schilder's communication, is here published for the first time.

In 1923 a case was admitted into St. George's Hospital under Dr. Collier, which in its clinical picture so closely resembled the former case that it was during life publicly demonstrated by him as a case of Schilder's disease. The pathological investigation showed that it was a typical case. This we believe is the first occasion on which the disease has been recognized during life.

The object of this communication is to record these two cases, and to show that in a considerable number of the recorded cases the clinical aspect of the disease has been so nearly identical with that of these two cases as to allow us to lay down with every confidence and for the first

time a clinical description of Schilder's disease which will be of value as an aid to the recognition of the malady in the future. We hope also that the description of the morbid anatomy and the numerous illustrations we publish may enable the reader to recognize the anatomical picture should he encounter it.

Argument.—The bald clinical aspect divested of minute details which we wish to lay down is as follows:—

A malady usually occurring in children and young subjects with no tangible causal factors or antecedents. The onset is a few days, the course progressive with some remissions to a fatal issue, the duration from a few months to three years. The chief early sign is cerebral blindness which becomes complete, to which is added mental reduction and increasing spastic paralysis. Unsteadiness from parietal involvement and deafness from temporal involvement may be conspicuous. The amentia increases and passes into coma which terminates the illness. The condition, usually bilateral, may commence on one side or may be confined to one side.

The pathological picture, which has been well known since Schilder's monograph appeared in 1912, well explains the symptomatology. It is that of a massive affection of the white matter of the cerebral hemispheres, considered to be toxic in origin and inflammatory in nature, and characterized by the disappearance of the myelin, the axis-cylinders remaining for a long time intact, though these eventually perish; with comparatively little lymphocyte exudation and not very conspicuous glial reaction.

This affection, commencing bilaterally in the white matter of the occipital lobes, spreads forward through the white centres by contiguity. It spares the cortical grey matter and subsulcine arcuate fibres and the basal ganglia, either completely or at least for a very long time. It advances throughout the central white matter of the hemispheres and may descend along the white matter to the capsules, crura and pons. It affects last of all the white matter of the frontal and temporal poles, and according to the stage of the disease at which death occurs these regions may be either completely spared or affected to a lesser or greater extent.

The following synopsis of symptoms in the recorded cases in order of their development shows clearly how nearly the clinical aspect has conformed to the description which we here put forward as characteristic of the disease. Any peculiarity in the pathological findings is also noted.

COLLIER and GREENFIELD (1).—Male, aged 7. Rapid failure of vision, hearing and mentality. Two fits. Ten weeks later a third fit followed by rapid developments of general spastic paralysis. Complete blindness with normal optic discs and active pupils. Universal spastic diplegia. Extreme emaciation. Duration, nine months.

The lesion was advanced and typical. The basal ganglia were invaded to some extent.

COLLIER and GREENFIELD (2).—Female, aged 5. Failure of vision progressing to complete blindness. Unsteadiness but no other sign for several months, then spastic paralysis of the legs, which subsequently invaded the whole body. Progressive amentia and emaciation. Optic discs normal and pupils active throughout. Duration, fifteen months.

The lesion was typical.

CENI, 1896.—Female, aged 9. Onset slow with confusion of mind and inability to read, gradual diminution of visual acuity to complete blindness. Bilateral unsteadiness followed by universal spastic paralysis, becoming intense. Some headache. Optic discs and pupils normal throughout. Duration, six months.

The lesion was typical.

HABERFELD and SPIELER, 1910.—Child, aged 7. (Another child of the same parents died of a similar malady at the age of 8½.) The illness commenced with failure of vision, inattention in school, apathy and great decrease in intellectual capacity, progressing to complete blindness, aphasia and amentia. Marked sweating. After four months, weakness and spasticity of the limbs appeared and progressed to a complete spastic diplegia. Some extensor spasms. Optic discs always normal and pupils reacted throughout but somewhat sluggishly. Wassermann reaction negative. Duration, two years.

Lesion typical, but in addition the central cortex showed diminution and disappearance of the cells of Betz and some gliosis. Two separate sclerotic foci were found in the spinal cord.

SCHILDER, 1912.—Female, aged 14. She was brought to an eye clinic because she had begun to see badly and because her mental state was deteriorating. She vomited frequently and had headache. Complete altitudinal hemianopia. Slight papillœdema. Wassermann reaction positive in patient and mother. Four weeks later all light perception was lost but the pupils reacted. Complete right hemiplegia and aphasia followed by amentia and emaciation. Duration, five and a half months.

Lesion typical, but while it had completely involved the occipital white centres on both sides, it had extended forward much more rapidly upon the left side to involve the left temporal and left central white centres, leaving those on the right side relatively intact. Hence the hemiplegic spastic paralysis in place of the usual diplegic spastic paralysis.

BOUMAN, 1924 (1).—Female, aged 32. After uncomplicated childbirth giddiness, visual disorientation and failure of vision. Left hemianopia rapidly

progressing to complete blindness. Congested discs and headaches but no optic neuritis. Trephined for occipital tumour and nothing found. Thereafter progressive bilateral spastic paralysis and great mental reduction. Pupils active throughout. One epileptic fit. Duration, eight months.

Lesion typical in the brain, but there were small patches of demyelination in the brain-stem like those of disseminated sclerosis.

BOUMAN, 1924 (2).—Male, aged 20. Imbecile from childhood. For a year he was noticed to be unsteady in his gait. He then developed rapidly progressive bilateral spastic paralysis, during the onset of which he had fifty-two fits. A month later he gradually ceased to speak, became comatose and died. No note as to vision. Duration, three months or fifteen months.

Lesions very typical and advanced. The white centres of both hemispheres were universally involved and of gelatinous appearance. There is no note as to the condition of vision of this patient; but from the extreme involvement of the occipital white matter on both sides, it does not seem possible that any vision could have persisted.

ROCHON-DUVIGNAUD and VALIERE VIALEIX, 1923.—Female, aged 22. For a few days her eyes became foggy, then in an hour or so she became quite blind in the left eye (? left hemianopia) and two days later in like fashion she became totally blind (? right hemianopia). Slight papillœdema and headache. Decompression for occipital tumour and nothing found. Thereafter right-sided convulsions and gradual onset of spastic diplegia. Emaciation. Torpor. Coma. Duration, forty-one days.

The lesion found was of a nature evidently unknown to these authors. They describe it as an encephalomalacia differing from all the forms of encephalomalacia with which they were acquainted by the complete absence of any signs of blood extravasation. They were sure it was not a condition of encephalitis lethargica, although lymphocyte cuffing was very conspicuous.

CASSIRER and LEWY, 1920.—Female, aged 37. Onset sudden in the night with fits. Three days later diminution of visual acuity progressing in a few weeks to almost complete blindness. Slightly swollen discs with a few points of hæmorrhage. No headache or vomiting. Pupils react normally. She improved remarkably for a time under mercury and thereafter relapsed rapidly. She became mentally reduced and without memory. At the end she was blind but her pupils reacted and the discs were described as pale and very slightly swollen. She died after a trephining. Duration, ten months.

Exception may be taken to this case, since the authors described the condition as one of glioma. Both the clinical and pathological findings, however, were very similar to those of encephalitis periaxialis, and this case is claimed by most observers to be of that nature. But that the clinical course was cut short by the operation, the end picture of this case would surely have been one of spastic diplegia owing to the extension forward of the lesion which had severely involved the occipital and temporal white centres.

STAUFFENBERG, 1918.—Female, aged 21. (Central scotoma in left eye with a high degree of papillitis, progressing to blindness of left eye. Two months

later diminution of vision in right eye with normal fundus. Thereafter vision improved and the papillary reflexes were normal; retrobulbar neuritis was diagnosed by Hess.) A fit suggestive of occipital origin. Headache, vomiting, somnolence. Euphoria, inattention, forgetfulness. Visual agnosia. Left hemianopia followed by right hemianopia. Perception of light almost completely lost. Pupils reacted. Unsteadiness and loss of sense of position in limbs. Another fit. Bilateral anæsthesia appearing on the left side first. Bilateral spastic paralysis appearing on the left side first. Many more fits. Complete apathy. Death. The cerebrospinal fluid throughout the illness showed some increase of albumen and an increase of lymphocytes. Duration, eight months.

The lesion in the brain was typical. A separate lesion in the optic chiasma is figured.

Stauffenberg summarizes his case very clearly in these words: "A prodromal affection of the left optic nerve occurred, causing the papillitis of the left disc and retrobulbar neuritis which passed over by the chiasma to the right optic nerve. Thereafter an affection of the white matter of both occipital lobes occurred, first on the left side causing the hemianopia, and spreading rapidly forwards destroyed the parietal, temporal and central radiations in turn with the production of the bilateral anæsthesia, intense psychic deterioration and spastic diplegia."

HERMEL, 1920.—Female, aged $3\frac{1}{2}$. Wassermann reaction negative. The child gradually changed in behaviour, lost interest, ceased to play and spoke less and less. Unsteadiness of legs. Speech impossible. Spastic diplegia becoming severe. Pupils reacted. At the time this patient came under observation the mental state was so reduced that no examination of vision was possible. Duration, ten months.

The lesion was typical but very soft. The whole white centres of the frontal, central, parietal, temporal and occipital lobes were affected. The lesion was less intense in the extreme posterior parts of the hemispheres.

KLARFELD, 1923.—Female, aged 23. The onset was with headache. She became slow mentally and "could not think." Four months later she became unable to read and progressively developed right hemianopia, aphasia and apraxia. Following upon a fit she developed left hemianopia, with more headache and vomiting. The pupils remained active and the optic discs were normal throughout. The right side became paralysed and spastic. Duration, one year.

The lesion was typical and was confined to the oval white centres of both hemispheres. It was much more advanced in the left hemisphere than in the right, and was more advanced in the occipital regions of the hemispheres than farther forward. This is a good example of the lesion commencing earlier and advancing farther in one hemisphere than in the other, as the clinical picture demonstrates.

CLAUDE and LHERMITTE, 1920.—Male, aged 19. In August, 1915, weakness of the legs was first noticed. This progressed until walking was

difficult. The deep reflexes throughout the body were lost, and the plantar reflexes were of the flexor type. He improved considerably, but in December, 1915, when again examined, he was spastic in all the limbs with increased jerks and extensor responses, and had dysmetria in the movements of all limbs. He had occasional attacks of torpor. In June, 1916, vision was noticed to be failing, and he developed visual disorientation and apraxia, and speech became difficult. Sight failed progressively until he became quite blind. The light reaction of the pupils and the fundi were normal throughout. There were many remissions and exacerbations of the symptoms in this case. Duration, twenty months.

The lesion, we think, was typical, but there are no illustrations. With the exception of secondary degeneration throughout the whole pyramidal systems, no lesion was found below the hemispheres of the cerebrum. The lesion was of the oval white centres, with much demyelinization. Very conspicuous lymphocyte exudation within the lesion is described.

We cannot see the justification for the term, "à foyers successifs," which these authors apply to the pathological process in their case which they name "leucencephalitis," either from the clinical story or from the anatomical description. A process spreading from one original focus, as has been held for so many cases of encephalitis periaxialis, seems to us adequate to explain both the anatomical and the clinical picture.

REDLICH, 1913.—Female, aged 41. Onset with headache followed in order by left hemianopia, left hemianæsthesia and left hemiplegia. Slight papillitis in both eyes. Weakness of right sixth nerve. She improved remarkably during nine months' treatment with iodides, after which her symptoms became rapidly intensified.

A large lesion in which demyelinization was conspicuous occupied the white oval centre of the white hemisphere in its posterior two-thirds.

BLANDY (Cases 1 and 2).—The clinical accounts of these two cases, of which the pathological specimens were demonstrated before the Neurological Section of the Royal Society of Medicine, London, May, 1924, have not yet been published. We have the permission of Dr. Blandy to state that in both these cases the clinical picture corresponded with the type here put forward.

It will be clear from a perusal of the brief accounts of the sixteen foregoing cases, out of the twenty-four cases which we have abstracted in this communication, that two-thirds of all the cases which have been reported have corresponded more or less exactly to the clinical picture which we submit is the usual in this disease—that of a commencement with occipital blindness from a lesion of the occipital white matter, and thereafter a development of symptoms of cerebral ablation owing to the spreading forwards of the lesion to the parietal, temporal, central and frontal regions and to the corpus callosum.

The majority, if not all, of these cases could have been diagnosed with

ease and certainty upon a recognition of the clinical type which we lay down. It must be borne in mind that we have considered with great care the clinical records of these cases, but in the abstracts we have not always followed the author's line of reasoning, nor have we always been subservient to the letter of his text. Lest we should be convicted of pressing any of these cases into the clinical picture which we here lay down, we must here explain the method with which we have dealt with the published records by citing an example. Schilder's case was in every way typical clinically and pathologically, but he considered that the blindness was due to retrobulbar neuritis, and states that there never was any local defect in the visual fields, nor any hemianopia. Yet he figures with his earliest note a chart of the visual fields showing complete bilateral altitudinal hemianopia, just such a chart as one would expect from a bilateral lesion of the upper occipital white matter. His last note upon the condition of vision was, "No light perception but the pupils react to light," the sign-manual of occipital blindness. He found no retrobulbar neuritis on autopsy, but complete destruction of the occipital white matter on both sides, yet he never connects the blindness with the lesion of the occipital regions. We have, therefore, taken the line of obvious truth in recording his case.

We may be criticized for including in this series corresponding to our type the cases of Bouman (2), and of Hermel, for in neither of these cases was there any record as to the condition of vision. But in the latter case when the patient came under observation the physiological condition did not allow of vision being tested, and in the former case the patient was in an advanced state of dementia. In both cases there was severe bilateral destruction of the occipital white matter, and since the lesion in this part of the brain seemed to be the oldest and most intense part of the lesion, we consider that there must have been early loss of sight and that it is therefore justifiable to include them.

In the following cases the starting point of the spreading lesion was not in the occipital white matter, and the clinical picture was different from the one which we consider usual in this malady.

ROSSOLIMO, 1897.—Male, aged 16. Gradual onset with weakness of right face, hand and leg, and affection of speech, progressing to complete spastic paralysis and complete loss of sensibility on the right side. Right-sided twitchings. Diplopia, nystagmus and double sixth nerve paralysis. No headache, no visual defects, no vomiting, no optic neuritis. Death occurred after an operation for decompression.

The lesion was typical and was confined to the left middle white oval centre. There was another small lesion in the medulla oblongata.

BRAUN, 1922.—Female, aged 29. Headache, loss of interest, apathy, incontinence. Left hemiplegia becoming complete. Shortly before death left hemianopia was present. Duration, four months.

The lesion was typical. It was much more extensive in the right hemisphere, where it extended from the occipital region to the anterior central region. It crossed the corpus callosum widely and extended a certain distance in to the left oval centre.

JAKOB, 1915.—Male, aged 35. Found subconscious on a dungheap. No history was obtained. He was apathetic and completely disoriented in time and space. Speech unintelligible and utterances rare. Wassermann reaction negative. Gait unsteady. A year later he had several fits. There was no investigation of vision in this case and the clinical details are meagre. Duration, seventeen months.

The lesion was typical and had evidently commenced in and was chiefly confined to the frontal white centres.

SIEMERLING and CREUTZFELDT, 1921.—Male, aged 7. Well-marked bronze discoloration of skin. Onset with restlessness and progressive deterioration of speech. Gait became unsteady and spastic diplegia followed and became intense. One fit occurred. Pupils equal and reacted. Discs were normal. There was no note as to vision or sensibility. Atrophy of the adrenal glands was found.

The lesion was typical. It involved the white centres of the temporal and central lobes and extended down into the pons. There was a similar destruction of the white centre of both cerebellar hemispheres, and there were other separate foci.

MARIE and FOIX, 1914.—Female, aged 28. Chronic tuberculosis of the lungs. At the age of 18 she gradually developed in the course of a few weeks a spastic quadriplegia with deterioration and then loss of speech. Six months later she improved remarkably and the improvement persisted for many years. Nine years later the spastic paralysis increased in both legs and in one arm and became complete. There was rapid mental deterioration and death soon followed. Duration not stated.

The lesion seems to us to be quite typical of encephalitis periaxialis. The white centres of the occipital, parietal, temporal and posterior central region were completely involved in both hemispheres. The process was one of demyelination of the white matter with little reaction in the adventitial sheaths and but mild glial reaction. The cortex and subcortical arcuate systems were not involved. There was no lesion in any part of the nervous system below the cerebral hemispheres, apart from the secondary degeneration of the pyramidal tracts. The lesion was most destructive in the occipital region.

This case is difficult to comprehend since the clinical account contains the bald statement that vision was normal. Yet the anatomical account and the good illustrations show clearly that the whole white matter of both occipital lobes was devoid of myelin and was in reality the oldest part of the lesion. Marie seeks to explain this discrepancy by arguing that function continued in

the bare axis-cylinders of the demyelinated areas. Yet in many of the recorded cases, as in our two cases, complete and long-lasting blindness was present with no greater lesion in the occipital white matter than was present in Marie's case.

Possibly there was some discrepancy in the clinical history of this case. There is but one clinical note without date, and there are no continuing notes. It is not recorded when this patient died, nor how long after the clinical record was taken. There was no detailed examination of vision. It is possible for the lesion of this disease to advance very rapidly and destroy very intensely in a short time. As all the other recorded cases show a strikingly exact correspondence between the clinical picture and the anatomical findings, and since in Marie's case the anatomical description is beyond reproach, we think it justifiable to call into question the adequacy of the clinical description.

WALTER, 1917.—Male, aged 40. Onset with loss of interest and euphoria. Three years later he was completely demented. Wassermann reaction negative. There were no visual changes. After this he gradually developed bilateral spastic paralysis and died.

The lesion was confined to the frontal and central white matter of both hemispheres.

HENNEBERG and KRAMER, 1916.—Female, aged 43. Onset with paræsthesia and loss of feeling in the left hand which spread to the whole left half of the body, and loss of taste in left side of tongue. Subsequently left hemiplegia. Considerable improvement for a time. Exacerbation with diplopia owing to right sixth nerve paralysis. Duration, eighteen months.

There were two lesions, the one in the white centre of the right parietal and central lobes extended to the cingulum and affected a considerable area of the corpus callosum, the other in the medulla oblongata, extending in the region of the right pyramid from the upper point of the crossing to the middle of the pons. There were also two very small lesions of the medulla oblongata.

KALTENBACH, 1922.—Male, aged 25. He came under observation with bilateral spastic paralysis and with much psychic change and euphoria. Fine tremor of hands and incontinence of urine. He died in a condition of general spastic paralysis and complete dementia. Duration, one year three months.

The lesion was typical and affected the whole of the white centres of both cerebral and of both cerebellar hemispheres. The grey matter of both cerebrum and cerebellum was intact, and the subsulcine arcuate fibres were preserved. There were no lesions in the brain-stem or spinal cord.

These cases are of great interest and importance, for they point out that though the lesion of encephalitis periaxialis usually commences in the posterior region of the hemisphere and spreads forward thence, yet it may in fact take origin in any part of the white matter and extend, sometimes narrowly and slowly, sometimes widely and quickly. The clinical pictures have corresponded with the site of the lesion, and

with the direction of its extension. In the cases of Jakob, of Walter and of Kaltenbach the lesion was frontal in origin. In those of Rossolimo, of Marie, and of Braun it was central in commencement. In the the case of Siemerling and Creutzfeldt, it began in the temporal region and extended into the central regions. In the case of Henneberg it obviously started in the parietal region and extended to the central regions and also deeply along the capsule to below the thalamic level, so producing the deep hemianæsthesia. Siemerling and Creuztfeldt and also Kaltenbach show in their cases that the white centre of the cerebellum may be affected in exactly similar fashion. The existence of multiple lesions in some of the cases in this and in the previous list shows beyond all controversy that more than one lesion, and sometimes many lesions, may exist, as was proved in Henneberg's case. Though they are the exception, yet from the nature of the morbid process, which is considered to be of toxic inflammatory nature, one would expect multiple lesions. Indeed the symmetrical affection of the two cerebral hemispheres in so many of the cases suggests that the malady starts as two symmetrical foci in the two hemispheres, rather than that it always extends from one hemisphere to the other by contiguity, via the corpus callosum, as many authors have maintained. While we support the extension of the lesion by contiguity and consider that some authors have proved the extension of the lesion from one hemisphere to the other by way of the corpus callosum, yet we are firmly of opinion that the anatomical findings negative such extension in many of the cases and support an original bilateral commencement.

We have thought fit to exclude from this consideration of the published cases some of the earlier cases recorded before the days of adequate histological methods, and also certain cases of which the reports either upon the clinical or upon the pathological side are inconclusive, namely, the cases recorded by Beneke, Schupfer, Heubner, Neuberger (two cases without clinical records), Schröder (Case 4, and possibly Case 5), Schmaus, Strumpel, Krabbe and Weiss, though we have no doubt that most of these cases were examples of encephalitis periaxialis.

Consideration of the Symptoms in Detail.

Headache.—This symptom has been frequently recorded among the cases, both at the onset and at any time in the course of the malady ; in Stauffenberg's case it was prominent and troublesome. In our cases, as in many others, it has been completely absent.

Vomiting.—In a few instances this has been a prominent symptom but in the majority of the cases it has not occurred.

Optic neuritis.—This has been reported in a good many of the cases and has given rise to the diagnosis of tumour and to decompression operations. It amounts at the best to a very mild degree of papill-œdema, which may be transient or may persist throughout. It is often absent. In only one case, that of Stauffenberg, has a high-grade papillitis occurred, and then in one eye only, the other being quite normal. This was diagnosed by Hess as part of a retrobulbar neuritis, and a retrobulbar lesion was found at autopsy and figured in the report. In more than one case "well marked" optic neuritis has been recorded, though the highest point of disc was measured + 4D., and the general fundus + 3D. and one such record is followed a few days later with the note: "Optic discs flat, temporal pallor," proving conclusively that not more than a slight papillœdema could have existed. A few hæmorrhages have been noticed in the retina in two cases.

The explanation of the occurrence of headache, vomiting and slight papillœdema in some of the cases seems to be that the intracranial pressure has been raised by swelling of the brain. Hypertension has been found on measurement in a few cases and the symptoms thereof relieved by lumbar puncture. The appearance of the brain in some of the cases, with its slightly shrunken aspect and enlargement of the ventricles, suggests a shrinking process, and this perhaps occurs throughout in a majority of the cases, since these do not show any of the above pressure signs.

Fits.—Of common but by no means usual occurrence in the symptomatology, a fit may be the first symptom to draw attention to the presence of illness, and may appear at any stage in the course of the disease, either singly, rarely or frequently repeated. The usual form is that of conjugate deviation followed by tonic and then clonic spasms, but sometimes tonic spasms alone have been observed. In one case only has there been a suggestion of a local occipital seizure. The occurrence of a fit has several times been followed by a rapid and severe exacerbation of the symptoms.

Pyrexia.—The course is usually apyrexial throughout. There is sometimes occasional pyrexia, and Stauffenberg's case was pyrexial throughout.

Cerebrospinal fluid.—This has been normal in the majority of instances, but is reported several times as containing an increased albumin content and a small excess of lymphocytes.

Wassermann reaction.—In only one case, that of Schilder (blood), has this been found positive in either the blood or the cerebrospinal fluid.

Cranial nerves.—The only abnormality that has been reported has been some degree of paralysis of the sixth nerve in a few cases; in at least two of these a separate focus of the disease existed in the medulla which at once explains the paralysis. In other cases it seems probable that some degree of conjugate deviation, so common to this disease, was interpreted as sixth nerve weakness.

The final position of the eyes in the state of terminal complete spastic paralysis was in our cases that of extreme upward deviation in the middle line, and this would correspond with the pathological picture of an "ultimum moriens" in the prefrontal region.

Smell and taste.—In one case smell and taste were lost upon one side; a very deep hemianæsthesia existed on the same side. (Henneberg and Kramer.)

Vision.—In our two cases the loss of vision occurred over the whole visual field equally, and this seems to be the most usual form of visual disturbance. Even when sight was reduced to faint perception of a strong light we could make out clearly that an intense point of light was perceived in every part of the visual field; and this result may be justly explained by the persistence of axis-cylinders. Altitudinal hemianopia occurred in Schilder's case. Homonymous hemianopia is the rule in the unilateral cases, while in the cases which commence earlier on one side, a hemianopia has occurred first on one side and then on the other with resulting universal blindness.

No instance of central scotoma from involvement of the extreme occipital pole has been reported, and this suggests that the place of election for the commencement of the lesion is in the centre of the occipital white matter. In some cases visual disorientation, visual agnosia and lack of recognition have preceded the blindness, or have existed in major degree when the blindness was as yet partial.

Hearing.—Auditory disorientation—the reference of all sounds to the less affected side—is an interesting phenomenon.

Mental condition.—In our second case at the stage where the blindness has become complete and before the advent of paralysis it was remarkable that the mental condition was so perfect and that the child took so little notice of her blindness and continued so happy. This may perhaps be described as euphoria. It has been noticed in other cases. A little later when the lesion had extended forwards, there was almost complete dementia. We would attribute this in major part to the involvement of the corpus callosum.

The mental changes, dullness, loss of initiative, euphoria, quietness,

and silence, progressing to dementia, have been most marked and earliest in the cases where the lesion has commenced in the frontal regions; here dementia has dominated the clinical picture, as in the cases of Jakob, Walter and Kaltenbach. They have often been well marked when the lesion commenced in the posterior regions of the hemisphere, and least pronounced where the central regions were first involved.

Sensory changes.—These have been mostly of the cortical type and described as unsteadiness, ataxy, dysmetria, astereognosis and loss of sense of position, such as one would expect with involvement of the parietal lobe. The extension of the lesion downwards along the capsule may cause much deeper loss, as occurred in Henneberg's case.

Spastic paralysis.—This has appeared in the legs first in most cases and for the reason, we submit, that the lesion commonly advances to the central region from behind. The first sign of its advent in our cases was the extensor response. With a frontal commencement the face has been first affected.

Course.—For the most this is regularly progressive. Periods of standstill are not uncommon. Marked improvement for a time occurred in the cases of Schilder (following the use of arsenic), Cassirer and Lewy (mercury), and Claude and Lhermitte (iodides), and Henneberg (iodides), while in Marie and Foix's case an interval of ten years of improvement is recorded.

Duration.—The shortest period from the first symptom has been forty-one days and the longest (excluding Marie's case) thirty-six months. With the same conclusion the average duration in seventeen cases was ten and a half months. In Marie's case after the rapid onset there was improvement, rapid for six months and gradual for over nine years, but the patient survived the second onset of symptoms by a few days only.

Diagnosis.—In those cases which present headache, vomiting and papillœdema the question of the presence of cerebral tumour must naturally arise. But the mild nature of the optic disc changes and their non-progress to the more intense degree of papillitis in the presence of signs of rapidly increasing and widely-spread cerebral destruction are important in making a distinction between the two conditions. Especially indicative in this connection is the bilateral affection of the hemipheres from the first in so many of the cases, which, in the absence of definite indications of brain-stem affection, is very much against the diagnosis of tumour.

The distinction from disseminate sclerosis is extremely important from the side of the morbid anatomy; it led Schilder, for example, to put the question: "Is this disease in reality a form of acute disseminate sclerosis especially incident in childhood?" But on the clinical side there seems to be little or nothing which is common to the two maladies, except the occasional signs of the existence of more than one lesion.

Description of the two cases which were personally observed:—

Case 1.—Walter S., aged 7, was admitted into The National Hospital under the care of Dr. Beevor on May 20, 1902, with the complaint that he had suffered with fits since October 11, 1901, followed by increasing weakness of the legs; he had been unable to walk since January, 1902. The family history gave nothing of importance and there was no story of fits or of any illness similar to the patient's malady. According to the personal history birth was normal and the child had been strong and healthy during the first six years of his life. He had had no illness until October, 1901, when his school teacher reported to the parents that the boy had not been well for a few days, for he was dull and did not see or hear properly. Six days later he was found in a fit which began in the right arm and became general. He had delusions for a fortnight after this fit, during which time his sight deteriorated rapidly. There was no sign of weakness of the limbs until January, 1902, when he had a second attack of general convulsions, after which his legs became progressively weaker and his speech dysarthric. A third fit occurred in March and since then he was unable to walk or talk. When admitted into hospital the child was much emaciated. He took no notice whatsoever of his surroundings and seemed to have no vision and no hearing. He sometimes uttered cries. Swallowing was difficult. He lay in any position in which he was placed and never moved his limbs. His head was slightly retracted, his trunk extended and his lower extremities stiff and slightly flexed at the hips and knees, and the feet and toes were dropped and in-turned. His upper extremities were quite flaccid and the jerks were not obtained in them. The knee- and ankle-jerks were brisk and the plantar reflexes were of the extensor type. The pupils were widely dilated and reacted to light. The optic discs and fundi showed no abnormality.

He lived for two months after admission, wasting progressively. There was considerable pyrexia for one fortnight while he was in hospital, for which no obvious cause could be found. He died of exhaustion on July 8, 1902. The total duration of his illness was nine months.

The autopsy was made by Dr. Collier six hours after death. The body was extremely emaciated, but no abnormalities were found other than those in the nervous system. The brain was much shrunken. It did not nearly fill the intracranial cavity and was everywhere separated from the dura by about

1 cm. thickness of cerebrospinal fluid. There was no sign of meningeal involvement or of vascular disease.

Examination of the surface of the brain showed marked shrinking of the convolutions with irregularity of level and "hill and hole" appearance. This atrophy of the gyri was most marked in the cunei and occipital regions, but it affected all the convolutions of the brain except the first and second frontal, and the orbital, uncinate and inferior temporal gyri on both sides.

FIG. 1.—Section at the level of the posterior colliculi. The demyelination of the white matter of the hemispheres is all but universal. The central tissue is much shrunken and the ventricle hard walled and tube like. The central tissue is dark in colour and gelatinous in appearance, but in it are scattered white opaque granules which coalesce into a mass on either side, below and lateral to the ventricles. The lesion is obviously older and more advanced in the upper (occipital) region than in the extreme lower (temporal) region. Destruction of the subsulcine arcuate bands is well seen in several places, especially in the left half of the section. The extension of the lesion into the crustæ is faintly seen.

A section through the brain after hardening in formalin, in the plane of the optic tracts at the level of the superior colliculus, showed an almost complete conversion of the white matter into a pale brownish somewhat translucent substance, almost as hard as cartilage, which contained in places masses of opaque white granules. The only recognizable white matter was that of the uncinate gyri and lower temporal gyri, and even these showed a relative degree of the same change. The subsulcine thin curves of white matter were, however, conspicuously exempt in places and stood out in high contrast to the gelatinous-looking central tissue (fig. 1). A section in the same plane at the level of the posterior commissure revealed an even more extensive change in

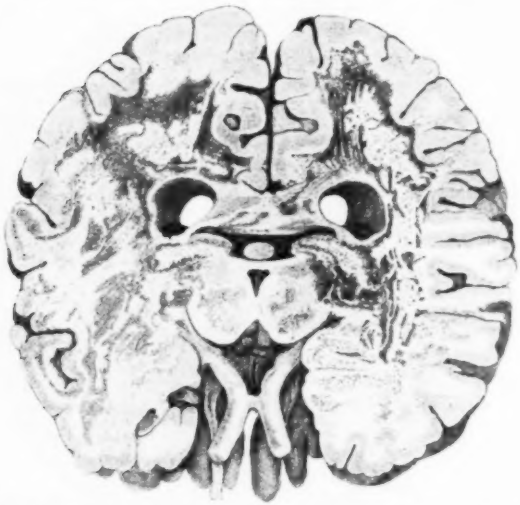


FIG. 2.—Section through the posterior commissure. The destruction of the central white matter is even more intense. The posterior end of the corpus callosum is severely affected. The usual limits of cortex and central matter are lost in many places, especially on the left side. The invasion of the basal ganglia is well shown. The lesion in both crustæ is very obvious.

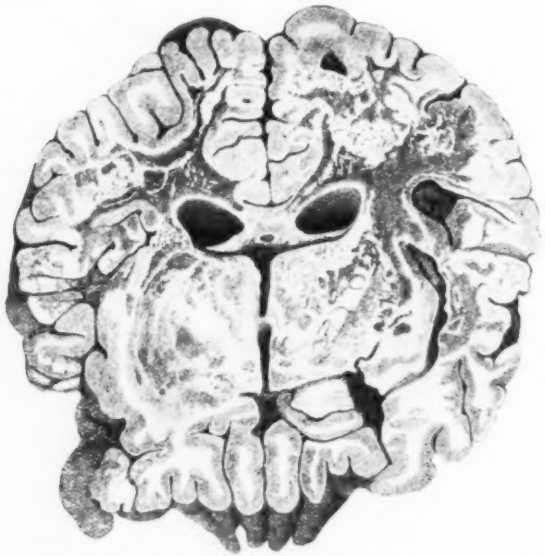


FIG. 3.—Section through the middle commissure. It shows the complete involvement and great wasting of the corpus callosum and the invasion of the capsules and basal ganglia. The orbital convolutions are almost unaffected.

the central white matter, which was everywhere much reduced in bulk and converted into a half-transparent brownish-grey substance. The posterior end of the corpus callosum was brown and translucent, and the corpora striata and posterior ends of the optic thalami were not recognizable. The internal capsules were markedly affected, as were also both crustæ, and the change could be traced throughout the brain-stem in the pyramidal tracts by the unaided eye (fig. 2). The posterior parts of the basal ganglia were seriously involved (fig. 3). Sections in the same plane at levels farther forward showed much less change;

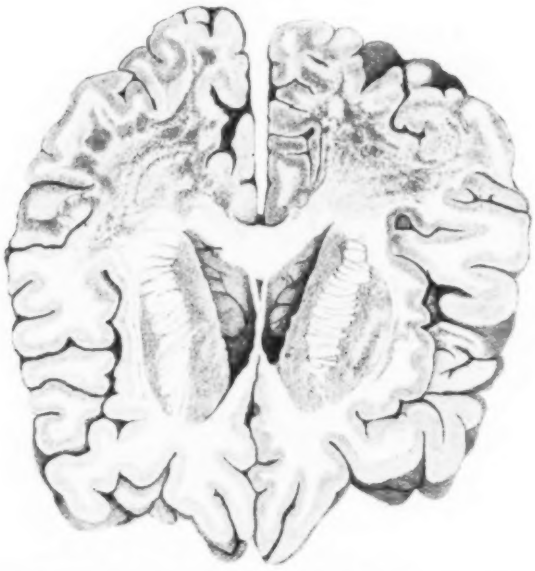


FIG. 4.—Section through anterior pillars of fornix. The contrast between the completely normal appearance below the level of the corpus callosum and the complete destruction above this level is well shown. The lesion is seen invading the corpus callosum from the sides, especially on the left side where it has almost reached the middle line.

at the level of the Rolandic fissures only the white matter dorsal to the corpus callosum was involved, but the latter structure was here almost normal, while at the level of the anterior end of the caudate nucleus the only disease was in the white matter underlying the marginal convolution on either side (figs. 4 and 5).

The grey matter of the cortex was thinner than normal in the more affected regions, but there was not nearly the same degree of change in the cortical tissue as was present in the underlying white matter.

The lateral ventricles were dilated and were tube-like with hard walls.

There were no gross changes in the brain-stem and spinal cord other than

the already mentioned affection of the pyramidal tracts. Examined by the Marchi and Kultschitsky-Pal methods, the tracts descending from the hemispheres showed almost complete degeneration throughout the brain-stem and spinal cord.

Unfortunately, owing to illness and to a change in the post of pathologist at The National Hospital at this time, July, 1902, this case was not further examined histologically and the material was lost.

FIG. 5.—Section through the frontal pole and forward end of corpus callosum. The earliest stages of the lesion are well shown in the grey discoloration of the oval centres.

Case 2.—Ivy K., aged 5, was admitted into St. George's Hospital under the care of Dr. Collier on November 22, 1923, with the complaint that she was blind in both eyes and that she had difficulty in walking unaided. She had been perfectly well and strong from the time of her birth up till the age of $4\frac{1}{2}$. Six months before admission her mother first noticed that she walked uncertainly, and for this trouble she was taken to Sydenham Hospital where failing vision was discovered. The sight became progressively worse and the gait more unsteady till the time of her admission to hospital. There had been no headaches, no fits and no other symptoms, nor had there been any mental change or impairment.

Condition on admission.—She was a bright, healthy-looking child of normal and acute mentality. Her speech was unaffected. She was well nourished and the thoracic and abdominal viscera and their functions

presented no defects. Vision was reduced to faint perception of strong light, but no more intense loss of any part of the visual field was made out. The pupils were of normal size and reacted well to light. The ocular movements were perfect. There was no defect of smell, hearing or taste. The functions of the other cranial nerves were normal. The upper extremities were used perfectly. The lower extremities were slightly spastic and ataxic and the feet were a little dropped and in-turned. She was able to walk, but her gait was characterized by lack of confidence owing to the blindness, and was also definitely spastic and ataxic, the ataxy suggesting a cerebral defect. The knee-jerks and ankle-jerks were obtained with great difficulty and the skin reflexes of the trunk were absent throughout and the plantar reflexes were of the extensor type. No objective defects of sensibility were detected. The cerebro-spinal fluid was normal and the Wassermann reactions in this fluid and in the blood were negative.

She remained in hospital nineteen days and during this time presented a bright and normal mentality. There was no headache nor vomiting. The light perception became extinguished and the lower extremities slightly more spastic. There was no pyrexia.

She was not seen again until eight months later, when she was readmitted into St. George's Hospital with the story that during this interval her lower extremities had gradually become very stiff and quite useless and that later the upper extremities became stiff and paralysed. Little by little she ceased to speak and lapsed into complete mindlessness and almost immobile spastic paralysis.

On admission she presented a universal, almost immobile spastic paralysis and made no response to any form of stimulation, except the imperfect and difficult swallowing of liquid food placed in the mouth. She seemed completely mindless and made no response to auditory or any other form of sensory stimulation. She lay upon her back, her head retracted, her eyelids widely retracted and her eyes in extreme deviation in the middle line. The elbows were firmly adducted to the trunk and the hands were held together with fists tightly clenched, but away from the sternum. The trunk was in rigid opisthotonos. The lower extremities were rigid, extended and adducted, with the feet dropped and in-turned. The aspect was characteristic of the "attitude of adoration" often seen in advanced and spastic diplegia. The optic discs were quite normal. The pupils reacted briskly to light. The conjunctival reflexes were never obtained. No other skin or deep reflexes were elicited, probably owing to the high degree of the rigidity. The sphincters were incontinent. She sometimes made a long wailing cry when she was moved.

Subsequently swallowing became more difficult. On the eleventh day after admission the temperature rose to 103° F., and two days later, June 17, 1924, she died quietly with the temperature at 105° F.

The duration of the illness was fifteen months.

The diagnosis of encephalitis periaxialis of Schilder was made on the second

admission into hospital and the case was demonstrated during life as an undoubtable example of this disease.

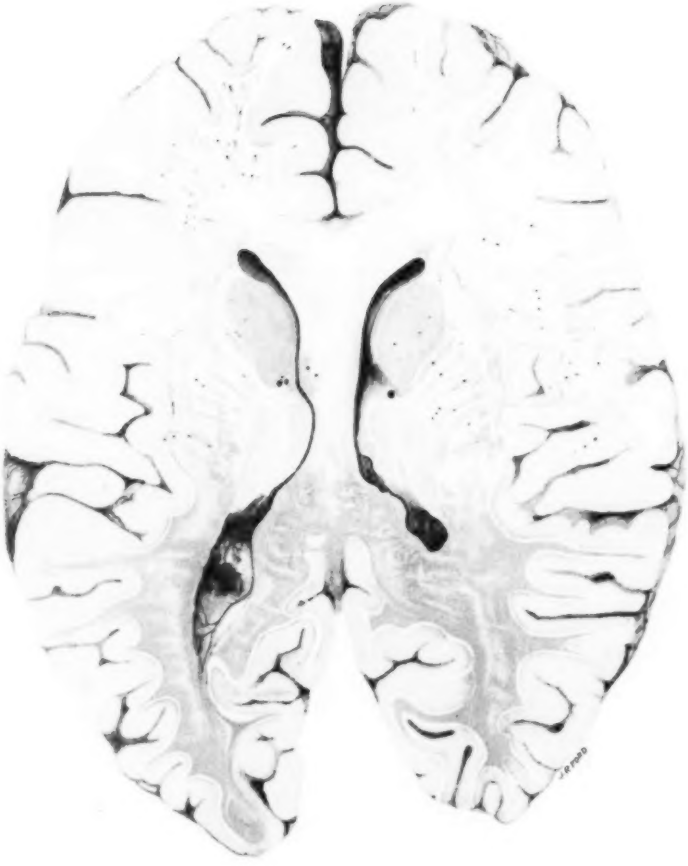
The brain was removed within twenty-four hours of death and fixed whole in No. 1 Kaiserling solution.

The external examination of the brain showed no abnormality except that the convolutions of the occipital lobe were narrower than normal and the intervening sulci rather wider. In this way an impression was created that the occipital lobes were more than usually convoluted. Horizontal section through the splenium and genu of the corpus callosum (Marie's *coup d'élection*) showed the typical picture described by Schilder. The whole of the white matter of the occipital lobes was affected with the exception of the subcortical white fibres which stood out prominently in their normal pallor. The rest of the white matter appeared as a pinkish grey substance which sank below the general level of the section. This condition affected also the external capsule and the posterior part of the internal capsule. In the frontal lobes the centrum ovale was less affected, and at first sight might have passed for normal; but on closer examination it was seen to have a mottled appearance, with patches of a pinkish-grey which were not sharply defined, as in disseminated sclerosis, but merged into the surrounding white substance by insensible gradations (see plate).

Sections made at lower levels showed the temporal lobes to be almost as severely affected as the occipital. Higher sections showed a progressive diminution in the extent of the disease. The corpus callosum was slightly affected in its posterior part. In addition to the general demyelination of the white matter there was seen a small rounded area of softening in the middle of the posterior limb of the internal capsule on the left side. This area appeared rather more yellowish and sunken than the surrounding white matter. The extent of the disease is well seen in the drawings (figs. 6 and 7).

By an unfortunate series of events we were only able to use for microscopic examination the lower half of the left cerebral hemisphere. This was cut into horizontal slabs 5 mm. in thickness. The highest available section passed through the middle of the corpus callosum, The lowest passed through the junction of the mid-brain and brain-stem; this slab included part of the red nucleus, the uppermost part of the substantia nigra, and parts of the optic tract and of the anterior commissure.

A few large slabs, each including one-third of the hemisphere, were mordanted by Weigert's primary mordant and embedded in celloidin.



Section of the brain of Case 2 showing the characteristic appearance after hardening in formalin. The lesion is most advanced in the occipital regions, where the pink-grey translucent colour and the almost complete destruction of the central white matter are well shown, advancing forward into the corpus callosum and into the capsules. The subsulcine arcuate bands are conspicuously preserved except in the extreme posterior pole. Farther forward the central white matter is almost universally affected by an earlier stage of the lesion.

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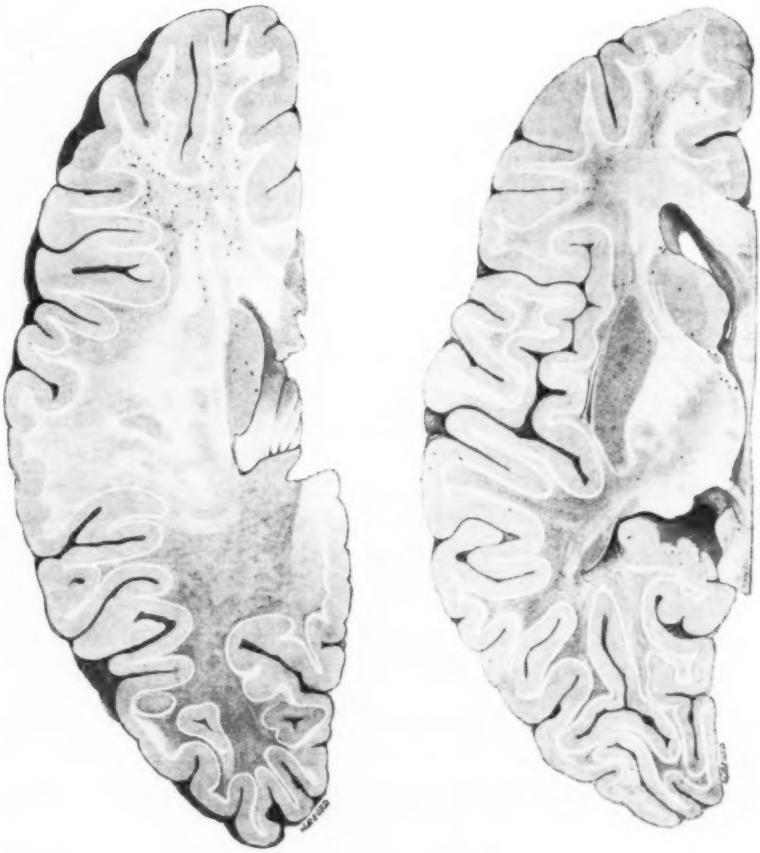

FIG. 6.—Section at the level of the tip of the caudate nucleus. The demyelination is well seen and is universal in the central white matter; it is much more advanced in the occipital region which is shrunken, and is earliest and shows punctæ cruentæ in the frontal region. The subsulcine arcuate bands are conspicuously intact, except for a space in the middle of the left border where they are almost completely destroyed.

FIG. 7.—Section through the middle of the insula. The cortex, subsulcine arcuate bands and the basal ganglia are intact. The lesion is seen invading the posterior part of the internal capsule, and also creeping along the external capsule to make the posterior region of the lesion continuous with the anterior part. The anterior part of the corpus callosum, for the most part normal, is being invaded from the central white matter.

The other slabs were cut into smaller pieces, from which a few frozen sections were first taken, and the remainder was then embedded in celloidin. The following staining methods were employed: Weigert's myelin method, and the Kultschitsky-Pal method on the large slabs; Nissl's stain, Pappenheim's methyl-green pyronin stain, alum hæmatoxylin with eosin and with van Gieson's counterstain and Turnbull's method for iron on celloidin sections; the frozen sections were stained by the Bielschowsky stain for neurofibrils, by the Kultschitsky-Pal stain for myelin, by Victoria blue for fibrillar neuroglia, and by Scharlach R. and alum hæmatoxylin for lipoids. A comparison of frozen sections from the same piece of tissue stained by these four methods proved to be of particular value in demonstrating the changes in the diseased portions of the brain.

These changes were shown to consist in:—

(1) A primary demyelination and later destruction of the axis cylinders in the centrum ovale, sparing to some extent the subcortical zone of white fibres and some of the radial cortical fibres.

(2) A very early, and in some places apparently primary, overgrowth of fibrillar neuroglia forming a feltwork which was particularly intense around the vessels, but elsewhere was finer. It was important to note that this neuroglial overgrowth everywhere spread into the inner layers of the cortex, where spider cells were seen lying among the large pyramidal nerve cells.

(3) A general infiltration of the white matter of the brain with round cells, all of which were apparently of neuroglial origin and most of which were engaged either in removal of altered myelin or in formation of neuroglial fibres. Associated with this there was a varying degree of perivascular infiltration with (*a*) fat-laden granule cells, (*b*) smaller and larger phagocytic cells of neuroglial origin, (*c*) undifferentiated small round cells. Some of the last may have been lymphocytes, although the cell body did not give the characteristic stain with toluidin blue or with pyronin. Many of them appeared to be small amœboid neuroglia cells. No plasma cells were anywhere seen.

These three kinds of change in the nervous tissue must be considered in rather greater detail.

(1) Demyelination and Damage to Axis-cylinders.

The apparent escape of the cortex and subcortical layer of white matter from the disease process was more apparent than real. The

cortex in fact showed a considerable loss of medullated fibres and the subcortical layer was also greatly impoverished by comparison with a normal brain (fig. 8). In the cortex there only remained some leashes of radial fibres, much more sparse than normal, a few of the more deeply placed horizontal fibres, and an occasional horizontal fibre of the line of Baillarger. Supraradial fibres were only seen in the pre-Rolandic cortex, and were very scanty there. In the visual cortex the line of Gennari could be seen with the naked eye in sections stained by the Kulschitsky-Pal method, but on microscopic examination it was seen to be very faint and only composed of the finest myelinated fibres. The subcortical

FIG. 8.—Horizontal section of occipito-temporal region showing demyelination of all the white matter except the subcortical band. Gennari's stripe can also be seen in the calcarine cortex. Slightly magnified. Weigert's myelin stain.

white matter also contained only fine fibres, and it was noteworthy that neither these nor what remained of the thicker fibres of the cortex gave any evidence of being doubly refractile. The radial fibres of the cortex as they passed more deeply into the white matter of the occipital and temporal lobes became at first beaded and twisted and then broken up into irregular masses of myelin which still stained by Weigert's or Kultschitsky's hæmatoxylin, and with Scharlach R. took the same colour as the rest of the myelin. Even in the completely degenerated areas a few unhealthy looking myelin sheaths were still present, but the majority of the myelin appeared either as granules lying free or as

larger masses included in the cytoplasm of compound granular corpuscles.

The external capsule and the posterior half of the hind limb of the internal capsule showed a similar process of myelin destruction. In the external capsule the degenerated band was separated from the cortex on the one side and from the claustrum on the other by a similar line of thin myelinated fibres to that bounding the cortex in the occipital lobes. The fibres passing through the lenticular nucleus were practically unaffected; to the naked eye the globus pallidus appeared normally myelinated, but under the microscope the bundles of fibres passing through its posterior part were seen to be accompanied by numerous granules of free myelin. These probably represented the degenerated myelin sheaths of fibres which had traversed the degenerated area in the internal capsule on their way to the lenticular nucleus.

In the frontal lobes the myelinated fibres stained fairly well everywhere except in the cortex, where few fibres except those of the radial system remained. But throughout the frontal region free granules of myelin, increasing in number as one passed backwards, could be seen among normal myelinated fibres.

In the lower sections most of the fibre systems, including the optic tracts, the ansa lenticularis and the inner half of the crusta pedunculi, were normal. The only degenerated tracts were the outer half of the crusta and the anterior commissure, which were seriously affected.

Bielschowsky's silver staining method for neurofibrils showed that in the cortex and the subcortical white matter at least the axis-cylinders suffered less than the myelin sheaths. All through the cortex this method revealed a wealth of tangential and horizontal fibres as well as a greater number of radially disposed axis-cylinders than could be seen after myelin staining. The undamaged zone of subcortical white matter also appeared to be wider than in sections stained for myelin, but on penetrating more deeply into the white substance the axis cylinders were seen to become contorted and broken. In the most affected parts in the centre of the occipital and temporal lobes no sign of axis-cylinders could be seen except a few twisted fragments.

The cells of the cortex, as shown by Bielschowsky's method, were everywhere shrunken, containing very little cell body outside the nucleus, and no neurofibrillar reticulum beyond the fibrils passing directly from the axon to the dendrites. Some of them seemed to be bipolar, an appearance suggesting the loss of all but the apical dendrite. In some the nucleus lay quite eccentrically and even bulging from the side of the cell body.

Toluidin blue showed no Nissl granules in any nerve cells. This may have been due to faulty fixation and preservation, as the brain had been several months in formalin before we received it. An appearance which seemed to be more trustworthy than the loss of Nissl granules was the small size of the cell body and its shrinkage away from the surrounding tissue, leaving a clear zone outside it. This was very noticeable in the most severely affected regions of the brain, and was seen only here and there in the frontal cortex.

In the nucleus caudatus the larger nerve cells were degenerated, showing a reniform or shrunken nucleus which often lay in an eccentric position. The cell body was small and its outlines irregular; as a rule it was more globular than normal. Some of the cells were in an extreme degree of chromatolysis with an eccentric or almost extruded nucleus. The larger cells of the putamen were similarly but rather more severely affected. Many of them appeared as rounded shrunken bodies in which the nucleus and cytoplasm stained with almost the same intensity, and the central nucleolar condensation of chromatin could hardly be distinguished. That this appearance was not due entirely to faulty fixation was evident from a comparison of these cells with those of the neighbouring cortex of the island of Reil, which were much more healthy.

In the pallidum the cells appeared to be rather less affected; their nuclei were usually central and the cell bodies elongated. Here as elsewhere no definite Nissl granules could be demonstrated.

(2) Neuroglial Overgrowth.

The overgrowth of fibrillar neuroglia was very well shown by the Victoria blue stain (Anderson's modification of Anglade and Morel's method, *Journ. Path. and Bact.*, 1923, xxvi, 431). It consisted in the most degenerated areas of a fine feltwork of thin fibres among which lay numerous small nuclei. In areas where degeneration was more recent, as, for example, in the subcortical zone, in the external capsule and the white substance overlying the putamen, numerous spider cells and large fibre-forming glial cells were seen. The latter consisted of large oval cells 20 to 30 μ in diameter, with an oval or flattened nucleus at one pole, and a fringe of fine, ill-defined processes which usually arose from the opposite pole. Frequently these cells showed two or more nuclei; their cytoplasm was sometimes finely granular, but was for the most part clear, and with Scharlach R. took on a diffuse pale brick colour.

In such areas as this it was not unusual to see very large spider cells with cell-bodies measuring up to 40 μ and thick fleshy processes which could be traced among the finer neuroglial meshwork for considerable distances. Sometimes only one of these cells could be seen in a large area, whereas in other places several would be seen grouped together.

A somewhat different form of cell was seen in the external capsule and the white matter overlying the lenticular nucleus. These cells showed a small rounded nucleus and a relatively small cell body, scarcely larger than the nucleus, tapering at one side into a fairly thick process which in some of the cells was forked like a swallow's tail, while from the opposite side of the cell very numerous fine fibres arose. Frequently these cells showed double nuclei, and when this occurred the tail-like process was also double.

The frontal cortex showed only the earliest signs of neuroglial overgrowth, such as enlargement of the cell body or of the nucleus, or reduplication of the nucleus. In this region there was no evident overgrowth of neuroglial fibres. In the subependymal neuroglia some very large elongated spider cells were seen with cell bodies measuring up to 50 μ in length.

The neuroglial overgrowth in the posterior part of the internal capsule was represented by a dense thickening of the neuroglial strands which run transversely across it, in the meshes of which were seen clusters of four, six, or more of the "globoid" cells, to which we must now refer:—

(3) Phagocytic Cells.

(*a*) In all regions where myelin destruction was active, particularly in those regions where it appeared to be of more recent date, there were large "globoid" cells of peculiar character. Their nuclei were always multiple and sometimes were numerous, and were arranged as a chain of thin flattened nuclei under the capsule of the cell. In size these cells were remarkably uniform, the smallest being 30 μ and the largest 50 μ. Their cytoplasm was almost clear, or at most very finely granular, and with Scharlach R. only gave a diffuse pale-brick colour similar to that seen in the large fibre-forming glial cells. These globoid cells appeared to have considerable powers of migration, especially in regions where there was much myelin destruction, as in the occipital and temporal lobes. In these regions they were seen scattered sparsely through the tissues and collected in small clusters alongside the vessels. They could be traced into the subcortical zone of white matter, but not

into the cortex itself. In more recently damaged areas, such as the internal capsule and the part of the centrum ovale which overlies the lenticular nucleus, they were much more numerous; here also they often lay in small groups, particularly in the internal capsule where the transverse neuroglial fibres formed nests for four to six "globoid" cells (fig. 9). Their complete lack of cell processes was illustrated by the readiness with which they dropped out of frozen sections; in sections stained for neuroglia many of these nests were quite empty.

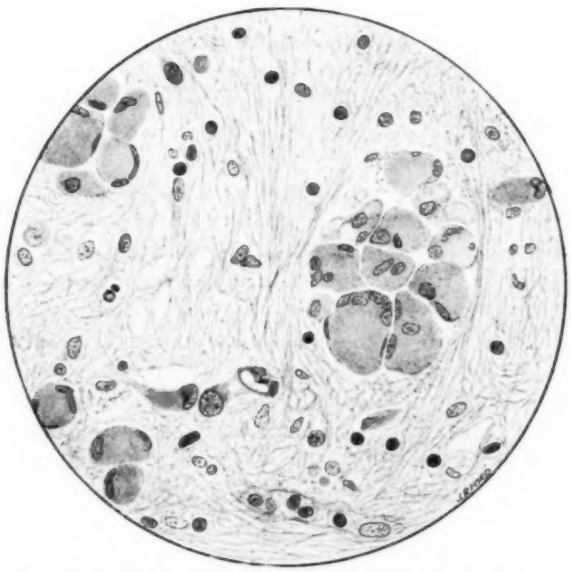

FIG. 9.—Section of posterior limb of the internal capsule, showing several collections of large "globoid" cells enclosed in a dense fibrillar neuroglial network. A few enlarged fibre-forming neuroglial cells can also be seen. (Hæmalum and van Gieson.) (Obj. $\frac{1}{12}$ inch. Ocular × 10.)

These cells are quite unlike any of the cells seen in Wallerian degeneration in the central nervous system, and do not correspond to any of the ordinary types of compound granular corpuscles. Their contents were never doubly refractile, and only occasionally granular. Such globoid cells, with chains of subcapsular nuclei, are occasionally found in gliomatous tumours, but apart from this they are very rare, and even in tumours they are never seen in the masses in which they occurred in this case.

(*b*) In addition to these larger cells there were numerous smaller cells measuring 10 to 20 μ, with a single-rounded eccentrically placed nucleus and more granular cytoplasm. These were seen particularly in the neighbourhood of the vessels, and formed the larger part of the small cells which took part in the perivascular infiltration. A few doubly refractile crystals of lipoid could be seen in some of these cells, but the majority of the granules did not stain intensely with Scharlach R. These cells appeared to be of the "small amœboid" neuroglial type.

(*c*) There was also a considerable number of typical compound granular corpuscles. These varied in size, but usually measured about twice the diameter of the smaller granular cells. In the temporal and occipital lobes they were found in the deeper layers only, collected either around the vessels or in the perivascular sheaths. In more recently degenerated areas, however, such as the centrum ovale overlying the basal ganglia, they were more numerous and more diffusely scattered. In the frontal poles also a few such cells could be seen.

The cellular infiltration along the anterior commissure was so intense that this structure stood out prominently to the naked eye in sections stained with toluidin blue. This was as evident in the part of the commissure which crosses the mid-line as in that external to the putamen. Microscopically, it was found to consist of an accumulation of cells of various kinds, most of which resembled the small undifferentiated granular cells which have just been described, while many were the nuclei of fibrillar neuroglial cells. In the neighbourhood of vessels there was also a considerable number of small uni- or multi-nuclear granular corpuscles, and the perivascular spaces were filled with these and the small granular cells. Globoid cells were scanty and of small size. A few large fibre-forming glial cells were also seen, and there was a general thickening of the fibrillar neuroglial network. Owing to the intensity of the cellular infiltration and to the large numbers of small cells taking part in it, we are inclined to regard the degeneration in the anterior commissure as being due to an actual spread of the disease into it rather than to Wallerian degeneration resulting from disease of the temporal poles.

Pathogenesis and Ætiology.

In attempting to form a conception of the pathogenesis of this curious disease, we are influenced to some extent by having had the opportunity of seeing the brains and some of the histological sections in

Dr. Blandy's two cases. In the first of these the disease appeared to be of more gradual onset than in our Case 2, for although the degenerated areas of the brain were of more leathery consistence, they had not reached the cortex over nearly so wide an extent as in our case. In her second case, which was that of an infant, the disease in the brain was evidently of recent date and affected only the central part of the white matter in the occipital lobes where the nervous tissue was soft and brownish. In this case the degeneration did not anywhere reach the subcortical layer of myelinated fibres. The histological picture in this case was that of a rapid degeneration of myelin with the formation of spaces between the myelin fibres not unlike that which occurs in the cord in subacute combined degeneration. There were numerous compound granular corpuscles loaded with fatty debris scattered irregularly through the tissues but not yet collected round the vessels. Except for a number of small amœboid glial cells in the tissue spaces there was no evidence of small-celled infiltration either in the tissues or in the perivascular lymphatics.

In her first case the appearance in the centre of the demyelinated areas was similar to that in our Case 2; it contained similar globoid cells and a rather more dense neuroglial overgrowth, but at the edge of this area where the disease approached the cortex of the brain there was a thick zone filled with fat-laden granular corpuscles. In this case there was considerable cuffing of some of the vessels by small cells similar to those seen in our case.

This cursory examination affords evidence that compound granular corpuscles play the chief rôle in the early stages of myelin transformation, and that at this stage small amœboid glial cells are also mobilized.

The large globoid cells which formed such a prominent histological feature in our case are evidently formed at a rather later date, and their freedom from fatty inclusions suggests that they have nothing to do with myelin destruction. But they are obviously migratory cells and seem eventually to arrive at the perivascular lymphatics. What happens to them after this we were not able to determine. That they are of neuroglial origin seems evident from their resemblance to some of the larger fibre-forming neuroglial cells. They appear to be the same type of cell as is described by Schilder as "grosse plasmareiche Gliazellen," and are figured by him as such in coloured drawings. He considered that some of the subcapsular nuclei belonged to parasitic or satellite glial cells, but of this we found no evidence. Owing to

their tardy appearance in the disease they cannot be considered as taking any active part in its causation, nor indeed is it wise, in the present state of our knowledge of the causes and processes of neuroglial reaction, to base any ætiological significance on their appearance. But it seems clear that (1) they are a cell type foreign to most other forms of myelin destruction; and (2) that they form a prominent and possibly an essential feature of this disease. We have not been able to find any cells resembling them in our cases of disseminated sclerosis, nor are they figured in Dawson's large monograph on this subject.

The other cell form which was particularly prominent in our Case 2 was the small amœboid neuroglial cell. In some respects these cells resembled the large globoid cells, and indeed there appeared to be transition forms between the two cell types. The early appearance of small amœboid neuroglial cells (for example, in Dr. Blandy's second case) suggests that they also may be an essential feature of this disease, and that at a later stage of their development they give rise to larger multinucleated cells of the "globoid" type.

The perivascular infiltration by small round cells has been held by many authors to be evidence in favour of a micro-organismal etiology. Although it was present in our case we do not consider that it necessarily had this significance, for no plasma cells were present and the majority of the small cells in the perivascular spaces were certainly not true lymphocytes. There can be no doubt that, in the brain at all events, a great variety of degenerative processes is associated with small-celled infiltration, and we have seen this in quite as intense form in gliomata and in the neighbourhood of vascular softenings resulting from non-syphilitic atheroma. According to Bertrand the mesodermal cells lining the perivascular spaces proliferate in response to a variety of stimuli, one of which is the degeneration of nervous tissue in the neighbourhood, so that in the region of a tract undergoing Wallerian degeneration we may see "as intense a perivascular lymphocytic infiltration as is found in epidemic encephalitis." If this be so the only proof of an organismal cause for small-celled perivascular infiltration in the brain is the presence of plasma cells.

We have already drawn attention to the resemblance of the large globoid cells to some of the cell types present in gliomata, and to the absence of these cells from most other forms of myelin destruction and neuroglial overgrowth. But in spite of this there seems to be no justification for regarding Schilder's encephalitis as being related in any

way to tumour formation. The symmetry of the process in the posterior half of the two hemispheres in the majority of the recorded cases, the sparing of the cortex and of the subcortical band of fibres, and the absence of any increase of brain bulk are strong arguments against any such assumption.

It seems to us that it is a disease affecting primarily the neuroglia of the centrum ovale, which, as is well known, differs in many respects from that of the cortex and grey matter. It seems certain that the nutrition of the myelin sheath and axo-plasma is closely dependent on the integrity of the neuroglia, just as in the peripheral nerves the reformation of myelin depends on the nucleated sheath of Schwann. If, therefore, we can conceive of a process affecting the neuroglial cells of the white matter only and spreading by continuity, we would get the picture of this disease, for the neurons of the grey matter would still derive their sustenance from the intact neuroglia present in it. The nature of this process must still remain a matter for speculation. The disease often seems to appear at the same time and to spread at the same rate in both occipital lobes, as though dependent on some noxious influence carried to the brain by the posterior cerebral arteries. This noxa may be organismal, or it may belong to the same order of growth as that responsible for the D'Herelle phenomenon, which, in its method of appearance and spread, presents certain analogies with Schilder's encephalitis.

REFERENCES.

BERTRAND, IVAN. "Les processus de désintégration nerveuse." Paris, 1923. (Masson and Cie.)

DAWSON, J. W. *Trans. Roy. Soc. of Edin.*, vol. L, Part 3, No. 18.

Notices of Recent Publications.

Studien zur Physiologie und Pathologie des Liquor cerebrospinalis, mit besonderer Berücksichtigung seiner örtlichen Verschiedenheiten im Zell-und Eiweissgehalt. Von Dr. med. Walther Weigeldt. Jena: Gustav Fischer. 1923.

This monograph, as its name implies, is directed to a comparison of the constitution of the cerebrospinal fluid as it is found in different regions of the ventriculo-subarachnoid system. In order to pave the way for this study, the author devotes the first half of the book to a discussion of vexed questions in relation to the physiology of the cerebrospinal fluid. In detailing the classical experiments on this subject he covers ground that is now well trodden, and if he quotes more Teutonic than Anglo-Saxon literature, he atones for this by accepting with catholic impartiality almost all the views which have been advanced in both languages. A good critical judgment is shown, however, in the order of importance in which he places the various factors which take part in the formation and resorption of the fluid. In this connection he gives short accounts of various clinical experiments which he has himself carried out. In some of these the details supplied are so meagre that the evidence carries little weight, but in his experiments on the effects of cerebral congestion he has shown, so far as we know for the first time, that the fluid formed by the choroid plexus under these conditions, in addition to being increased in quantity, is altered in constitution, having a lowered specific gravity and diminished protein percentage. Similar changes in the cerebrospinal fluid were found in three cases of compression of the superior vena cava by mediastinal tumours.

The origin of the cells in the fluid is also fully discussed, and the author shows by a comparison of the quantitative and qualitative cell counts on specimens of fluid taken from ventricles, cisterna magna and lumbar theca, that the cells come from the meninges rather than from the blood.

In the second part of the book the author shows that the cerebrospinal fluid in the ventricles may differ in pressure, protein percentage and cell count from that in the cisterna magna, and this again from that in the lumbar theca. In every case examined the pressure was highest (in the horizontal position) within the ventricles. Normally the ventricular fluid shows no cells and a much lower protein percentage than that in the subarachnoid space, and even in diseases of the brain such as glioma, epidemic encephalitis and general paralysis, the ventricular fluid often remains quite normal, although that in

the cisterna magna shows gross evidences of disease. A comparison of the ventricular with the subarachnoid fluid was made in thirty cases, and in only two of these, viz., one of brain abscess and one of cerebral syphilis, was the ventricular fluid more affected than the cisternal fluid. Finally, the author discusses the "fractional examination" of the cerebrospinal fluid obtained by lumbar puncture, and shows that in order to obtain satisfactory evidence of disease of the brain by this method it is necessary to drain off considerable quantities and to examine at least the first and the last portions of fluid removed.

The book thus contains a mass of material, much of which is new and interesting, and will well repay study by those interested in the cerebrospinal fluid.

Traité de Psychologie. Par Georges Dumas. Tomes i and ii. Paris: Félix Alcan. 1923-4. Price: tome i, 40 fr; tome ii, 60 fr.

The two volumes of this system of psychology which have been edited by Dumas and written with the help of twenty-four collaborators, all of whom are well-known psychologists, extend to more than 2,000 octavo pages. The aim with which it has been planned has been to present to all interested in psychology, either from the social or philosophical points of view, or as neurologists or psychiatrists, an exposition of the present state of our knowledge and bibliographies which will assist in the further investigation of any problem interesting to whoever may consult it. It is therefore a composite textbook in which each author, chosen to present one subject owing to his special aptitude or knowledge of it, expresses his own points of view. Such a division of labour, necessary though it may be in a work of this size, frequently results in a conglomerate of articles of unequal value, more or less detached from one another or connected together by the loosest ties, unless it is designed and controlled by the hand of an experienced editor. The most striking feature of these volumes, however, is the skilful arrangement of the different chapters and the manner in which they have been fused together into a more or less homogeneous system.

The first volume contains four books, of which the first is introductory and deals mainly with the anatomy and physiology of the nervous system; the second with the simpler elements of mental life; the third with sensory-motor associations, and the fourth with their organization. The second volume consists of sections on the systematized functions of mental life, as perception, memory, thought, and language, the more complex sentiments, volition and imagination; another section treats of mental synthesis, including consciousness, the subconscious, personality and character; and a section is devoted to allied subjects, as comparative psychology, sociology, mental pathology and pathological psychology. There is also an interesting section on the relation of the ductless glands to psychological processes, and a final chapter in which Dumas reviews the tendency to contemporary psychology.

The first features that strike the reader are the clear and concise style of most of the authors and the power of logical exposition displayed by almost all. In these respects these volumes contrast strongly with many psychological treatises in both his own and in foreign tongues that the English student may have to consult. But the completeness of most of the articles and the fairness with which various views are presented must be also emphasized. The whole treatise can be consequently recommended as a reliable work of reference, for it must be regarded as such rather than as a textbook. The bibliographies appended to the different chapters, though not overladen, will be found sufficient for most purposes.

It is regrettable that such a bulky work should appear in such an uncomfortable format, and that paper of such poor quality should have been chosen for its pages, but these are only minor details that do not seriously diminish its value. The absence of an index is a more serious defect.

Medizinische Psychologie für Ärzte und Psychologen. Von PAUL SCHILDER. S. 355, mit 9 Textabbildungen. Berlin: J. Springer. 1924. Price 2.90 dollars.

Year by year psychological textbooks increase in number, especially the smaller variety which purpose to be introductions to this science or to deal with one branch of it. Several of these have been either actually titled "medical psychology," or have been designed to supply the wants of medical practitioners interested in diseases of psychological nature or origin. In this aim they have, with few exceptions, failed.

The book under review belongs to a different category. The author admits that it is intended mainly for medical practitioners, and it will serve their ends because it looks at psychology from the point of view of the actual problems and phenomena of life; the claim that it is a "living psychology" is indeed justified. The section on the essential nature of speech, its development, and the psychological significance of the aphasic disturbances produced by cerebral disease, may be cited as instances of the direct appeal of the book to the practising doctor.

All aspects of the subject receive due attention, as the results of experimental psychology, the objective and subjective observation and analysis of the phenomena of mental life, cerebral pathology, and even psycho-analysis, which has in Schilder an ardent adherent. It is, however, by no means only a *potpourri* of facts learned by, or hypotheses formulated from, these various lines of research, for the author has a definite standpoint of his own and has skilfully incorporated within it all which he assumes may be accepted as truth and is pertinent to his subject. Certain sections of the book demand a considerable knowledge of psychiatry, though it is not in any sense of the term a textbook of psychopathology.

Each chapter and section is preceded by a short résumé of its contents, which makes reading more easy, and there is a valuable bibliography and an index.

Essays on the Evolution of Man. By G. ELLIOT SMITH. Pp. 154. Oxford University Press (H. Milford). 1924. Price 8s. 6d.

In this volume Professor Elliot Smith has reprinted three essays or papers which originally appeared between 1912 and the present year, and has furnished an introductory foreword on man's pedigree.

The first chapter, on the evolution of man, emphasizes the importance in the evolution of the human intellect of the steady growth and specialization of certain parts of the brain, especially of those portions concerned with vision, the impetus to the development of which may be found in the arboreal life of man's ancestors. The second essay is devoted to primitive man, and the third to the human brain. In the latter, the author's view on the significance in mental development of stereoscopic vision, which he believes was first acquired by the Tarsioidea, from which, according to him, the human stem is derived, is again put forward. The faculty of recognizing objects by their shape, colour and size, and of judging space, is denied to the lower animals, to the hawk that swoops and to the cat that springs unerringly on its selected prey.

It is an interesting volume, though it contains hypotheses which will require much more elaboration before they can claim general acceptance.

Injuries of the Spinal Cord and Cauda Equina. Medical Research Council: Report of the Committee upon Injuries of the Nervous System. Pp. 75. H.M. Stationery Office. London, 1924. Price 1s. 6d.

The object of the Committee which drew up this report was to collate the practical results of experiences of injuries of the spinal cord and cauda equina inflicted during the late war, and to present them in a form in which they can be applied to the treatment of such spinal lesions as are met with in civilian practice.

A considerable number of pages are devoted to elementary matters, such as the elements of anatomy of the spinal cord, the methods of examination of cases in which it is injured or diseased, and the distinction between symptoms of structural and psychical origin. The short sections on the state of the bladder and rectum in organic disease are, however, useful.

In the section on the localization of the lesion insufficient emphasis is perhaps laid on the more objective methods of investigation, as the distribution of the motor paresis and the reflex changes, while that on the recognition of

the degree of severity of the lesion is disappointingly brief. The chapter on treatment, especially of the paralysed bladder, and the discussion on the indications and contra-indications for laminectomy, will be undoubtedly useful.

Der Aufbau der Psychose. Grundzüge der Psychiatrischen Strukturanalyse. Von KARL BIRNBAUM. S. 108. Berlin: J. Springer 1923. Price 3s.

The aim of this book, which according to the preface is a first instalment to a more ambitious plan, is to analyse by clinical methods the structure of the various psychoses, and in this way to determine as far as possible the nature of the various elements of which each is composed and the different causal factors concerned in their pathogenesis.

It is an attempt at a scientific investigation of mental diseases from a somewhat different angle than has been hitherto followed, and one which promises to yield valuable results. The book can be warmly recommended to psychiatrists.

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TO

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